VOLUME 41 NUMBER 3

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The presence of chromatic aberration (color fringes) in bifocal segments is responsible for more unsatisfactory bifocals than all the other causes combined. When this aberration is present, words are fringed with colors, usually red or blue, which in itself is distracting. However, the most serious thing about a lens that has chromatic aberration is that the vision is not perfectly clear through any portion of the segment. This is true because the red rays are refracted less than the blue rays and the same point on the segment, therefore, has not one power but several, none of which necessarily bring the printed word into clear focus.

It is fundamental that all bifocals have some chromatic aberration inherent in their segments. The amount of this aberration, measured in diopters of chromatic aberration (written D. C. A.), can be calculated quite easily. In the hope that a better understanding of this major bifocal defect will be helpful we are giving below the formula for finding the D. C. A. found in bifocal segments, several examples and the maximum amount of D. C. A. that on the average will be tolerated.

Here is the formula:

$$\frac{D1}{V1} + \frac{D2}{V2} = 0$$

D1 and D2 represent respectively the power of the crown glass and of the segment button. V1 and V2 are, again respectively, the relative reciprocal dispersions of the crown glass and the glass used in the segment. When the values in the equation equal not zero but a number, chromatic aberration is present. The V value of crown glass is 60, of flint 36.8 and of barium crown glass 55.

Now let us take a lens with a + 2.00 add. In flint construction D1 is — 12.00 D, D2 is + 14.00 D, V1 is 60 and V2 is 36.8. Substituting these values in the formula and solving gives us .180 as the D. C. A.

When the bifocal under consideration is of one piece construction, D2 and V2 drop out of the formula, D 1 becomes the power (add) of the bifocal, and since one piece bifocals are made of crown glass, V1 is 60, in the case of a + 2.00 add ultex, the lens is found to have .033 D. C. A.

Below we have a table showing the amount of chromatic aberration in bifocals made with flint buttons, with barium crown buttons and in bifocals of one piece construction. It has been found that .05 diopters of chromatic aberration is allowable if no other factors add to it. By other factors we mean faulty surfaces, fusing defects and other mechanical errors. A bifocal that has more than .05 D. C. A. is to be regarded with suspicion and a bifocal with .1 D. C. A. or more is pretty sure to cause trouble.

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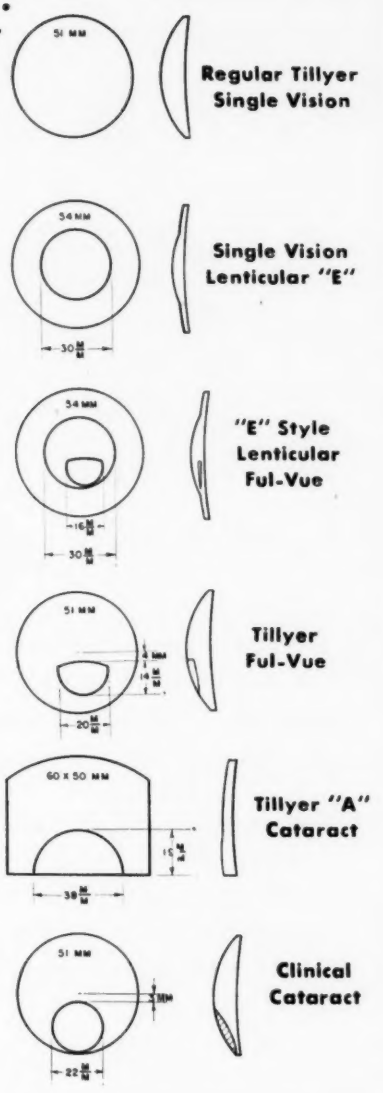

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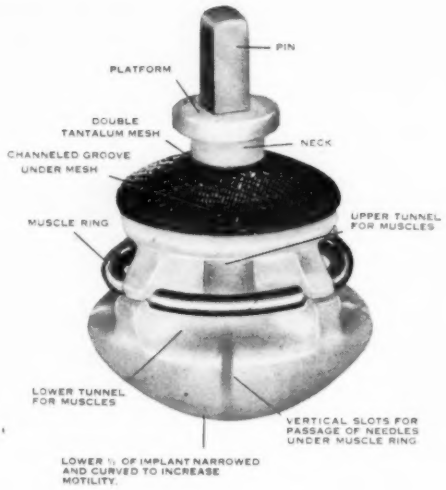

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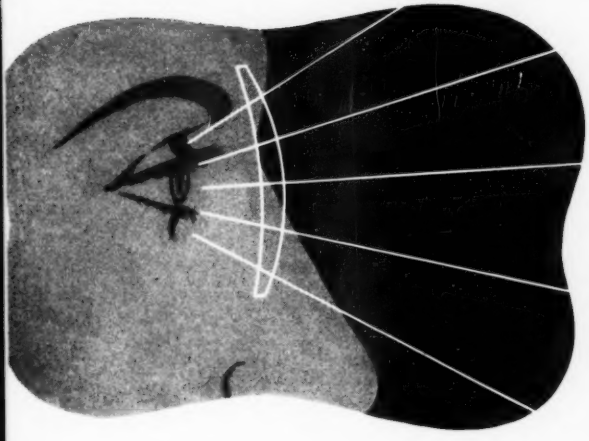

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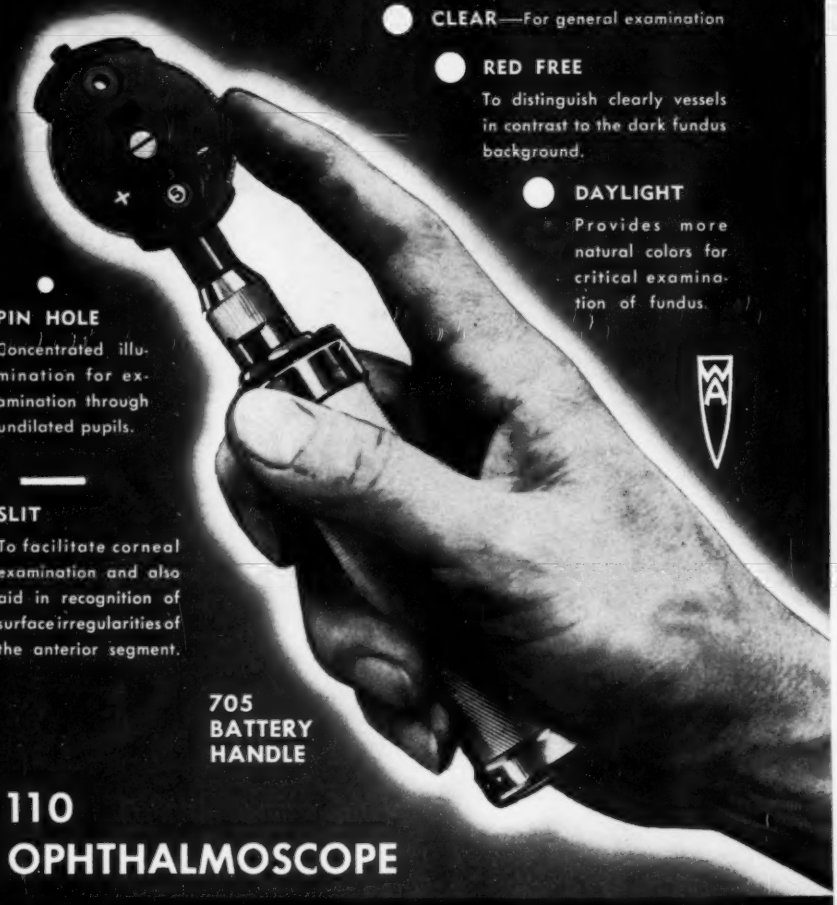

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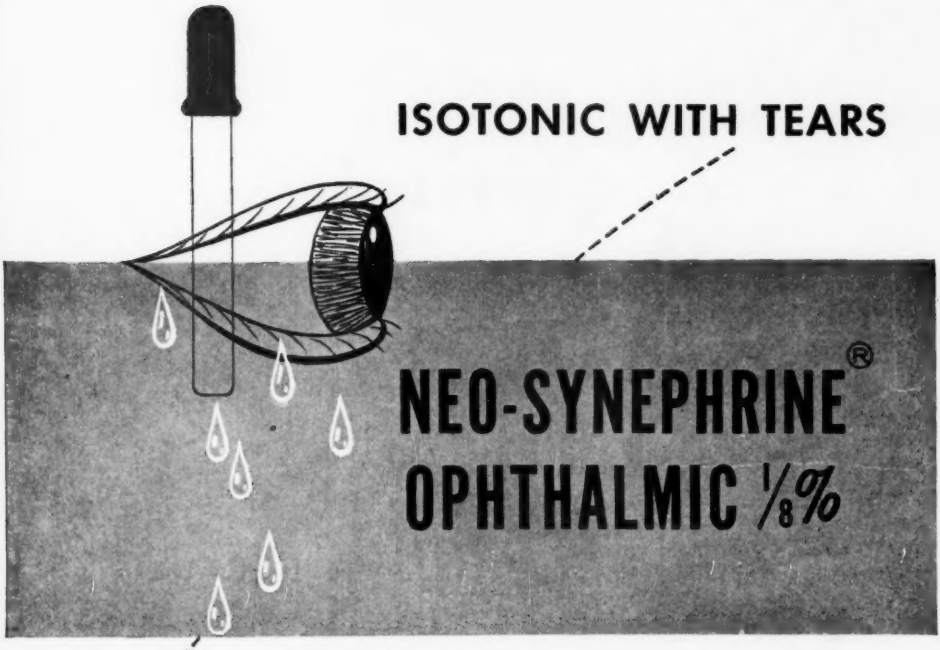

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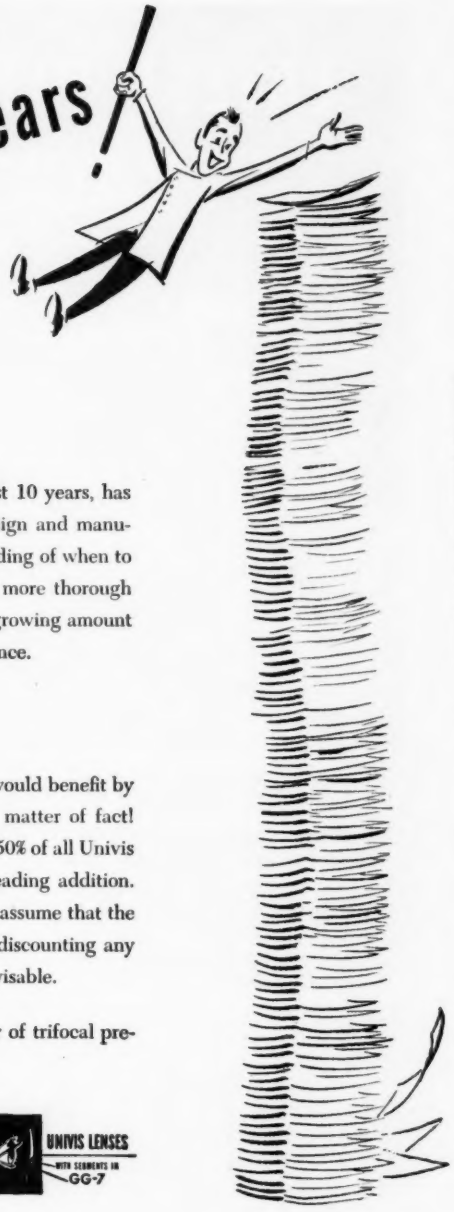

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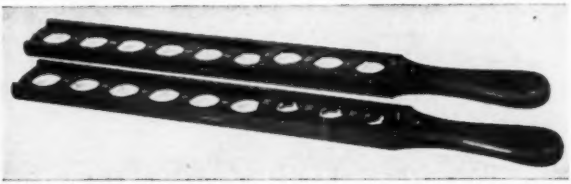

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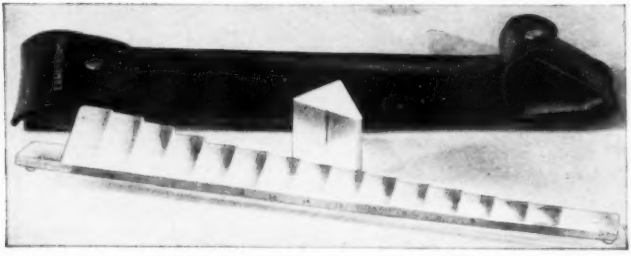

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PHARMACOLOGY AND TOXICOLOGY OF THE CORNEA

Contemporary Concepts

KENNETH C. SWAN, M.D.

PORTLAND, ORE.

DR. FRANCIS PROCTOR was keenly interested in physiologic optics; it is appropriate, therefore, that this first lecture should concern the cornea, the most important part of the optical system of the eye. The smooth surface, regular curvature and high degree of transparency which are responsible for the optical effectiveness of the cornea are maintained free of aberration by a series of unique physical and chemical balances. These delicate balances are dependent on the functional integrity of the various corneal layers. The functions of these layers are affected in diverse ways by drugs and poisons; consequently, discussion of the pharmacology and toxicology of the cornea necessitates consideration of the layers individually, as well as in relation to each other.

In classic descriptions of corneal histology, the epithelium is considered to be most superficial, but functionally the surface layer is the precorneal film. This film must not be dismissed as a simple aqueous solution. Normally, the precorneal film has both protein and mucoprotein components, in such a delicate physicochemical balance that a stable viscous film with high wetting properties and optical clarity is maintained. Its protein content is maintained by evaporation; at a concentration greater than that of the lacrimal secretion; however, the film never becomes so viscous that bubbles are retained to obscure vision because excessive evaporation stimulates an increased lacrimal flow. Likewise, if the precorneal film is thinned with a free flow of lacrimal secretion, evaporation and flow of excess tears into the lacrimal canaliculi soon reestablish a proper state of viscosity. The components of the precorneal film must constantly be replaced; otherwise, the film would become cloudy with the cells which are constantly being desquamated from the surface epithelium. In some patients an abnormal rate of desquamation causes rapid clouding of solutions under contact lenses.

From the Department of Ophthalmology, University of Oregon Medical School.

Delivered as the first Francis I. Proctor Lecture at the University of California, Dec. 20, 1946.

This lecture represents part of a study being conducted under a grant from the John and Mary R. Markle Foundation.

Many analyses have been made of the chemical and physical properties of tears; yet there is considerable disagreement. For example, Duke-Elder's statement that the osmotic pressure of the tears is equivalent to 1.4 per cent sodium chloride was disputed by Ridley, who found the tears to be nearly isotonic with 0.9 per cent sodium chloride.[1] These discrepancies are understandable when it is realized that the tears are not chemically or physically constant. For example, the normal flow of tears differs considerably from that produced by irritation of the fifth nerve or by direct stimulation of secreting nerves. This difference is particularly conspicuous in rabbits. The injection of a parasympathetic stimulant produces a white, chalky lacrimal secretion, in contrast to the usual clear flow (fig. 1). In situ studies of the p_H of the con-

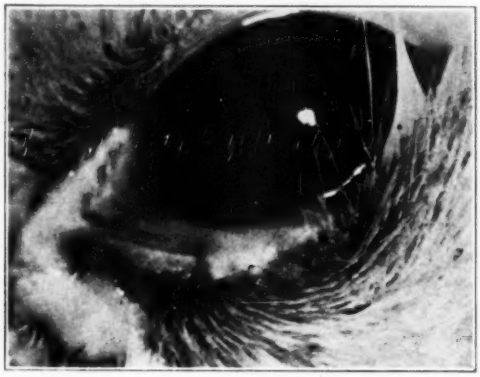

Fig. 1.—Rabbit's lacrimal secretion following administration of methacholine chloride U. S. P. (mecholyl chloride®).

junctival sac made with a glass electrode proved that the physical properties of the human conjunctival secretion also change with stimulation.[2] Initially this secretion is slightly alkaline, but when the tears start to flow from the mechanical irritation produced by the electrode the alkalinity increases rapidly (fig. 2).

The foregoing concepts of the precorneal film may be applied to pathologic conditions. It is frequently stated that the eye is adequately

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1932, vol. 1, p. 639. Ridley, F.: Chemical Composition of Tears: Clinical Significance of Composition of Tears, Tr. Ophth. Soc. U. Kingdom **54**: 541, 1934.

2. Swan, K. C.; Trussell, R. E., and Allen, J. H.: p_H of Secretion in Normal Conjunctival Sac Determined by Glass Electrode, Proc. Soc. Exper. Biol. & Med. **42**:296 (Oct.) 1939.

lubricated by the conjunctival secretion alone; however, the precorneal film undergoes chemically important changes with diminution or absence of lacrimal secretion. Biomicroscopy of the precorneal film reveals clumps of thick mucus, strands of desquamated epithelium and bubbles. Subjectively, vision is disturbed, and the eyes feel irritated.

Keratitis develops when the corneal epithelium is inadequately lubricated. Keratoconjunctivitis sicca typically occurs in women in the menopause or postmenopause and is associated with atrophy of the salivary, as well as the lacrimal, glands. Frequently arthropathy develops concurrently. Estrogenic therapy is commonly prescribed for this syndrome.[3] During the past several years, at the clinics of the

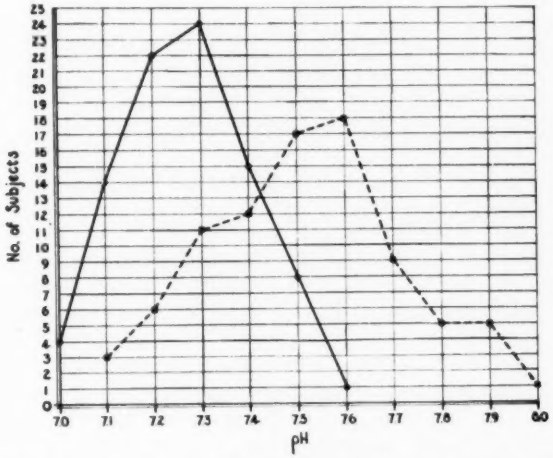

Fig. 2.—p_H range of conjunctiva in 88 normal adults. The solid line indicates the values before onset of lacrimation; the broken line, values during gross lacrimation.

University of Oregon Medical School, estrogens have been administered to 28 women with keratoconjunctivitis sicca occurring in association with menopausal symptoms. In all patients the precorneal film had become thickened and contained bubbles, strands of thick mucus and rolls of cellular debris. In 8 of the patients improvement occurred with estrogenic therapy, but all had mild disease of recent origin. In the remaining 20 women therapy did not affect the precorneal film, although in a number of instances there was restoration of the menstrual flow. In no case in which symptoms of the keratoconjunctivitis were

3. Fried, J. J., and Goldheizer, M. A.: The Endocrine Treatment of Keratoconjunctivitis Sicca, Am. J. Ophth. **27**:1003 (Sept.) 1944.

of two or three years' duration was a normal film restored. These clinical observations indicate that there is normally a hormonal control of lacrimation but that deficiency must be corrected early and adequately before irreversible atrophy occurs in the glands; i. e., early diagnosis must depend on the microscopic changes in the precorneal film which precede gross keratoconjunctivitis sicca. If the ophthalmologist defers his diagnosis until the latter develops, appreciable improvement is not to be expected from estrogenic therapy. Symptomatic therapy, such as artificial tears or closure of the canaliculi, then becomes necessary.

A second, and commonly overlooked, type of keratoconjunctivitis sicca results from the impaired lacrimal secretion which follows the inflammatory closure of the lacrimal ducts in some cases of chronic conjunctivitis. In such cases, the ophthalmologist must not be hasty in permanently closing the lacrimal canaliculi by cauterization, for lacrimation may recur with subsidence of the conjunctivitis and result in epiphora. Treatment of conjunctival inflammation and a temporary trial with artificial tears should always be made prior to the permanent occlusion of the canaliculi.

An entirely satisfactory substitute for the normal conjunctival and lacrimal secretions has yet to be devised, but a number of formulas for artificial tears have been described. Some, based on the theoretic chemical components of the lacrimal secretion, have contained dextrose, diverse electrolytes and buffers. Any preparation containing dextrose is certain to be unstable and favorable to bacterial growth unless preservatives are added. Moreover, these preparations are unduly complex. On the other hand, simple saline solutions or solutions of bicarbonate are unsatisfactory unless a viscous agent is added to give the preparation the cohesive and emollient properties of the normal precorneal film. Until recently, attempts have been made to adapt various compounds to these purposes, with only partial success. Acacia, tragacanth and gelatin have been most widely used, but they are chemically unstable, have high refractive indexes and are good mediums for the growth of bacteria and fungi. A synthetic substance, methyl cellulose, has shown considerable advantages over these naturally occurring gums as a conjunctival lubricant, cohesive and substitute for the precorneal film.[4]

Methyl cellulose is a water-soluble cellulose ether. Preparations with a high degree of purity and uniformity are available for ophthalmic use. There are several types, graded according to the degree of viscosity. For ophthalmic purposes the type with the highest viscosity (4,000 centipoises) is preferable, as only a small quantity need be added to aqueous solutions to increase the viscosity greatly without signifi-

4. Swan, K. C.: Use of Methyl Cellulose in Ophthalmology, Arch. Ophth. **33**:378 (May) 1945.

cantly altering its optical properties. One per cent aqueous solutions have a viscosity many times that of water, but are highly transparent and colorless and have a low dispersive power and refractive index (1.336), similar to that of distilled water (1.334). In addition, solutions of methyl cellulose are neutral, odorless, tasteless and nearly inert chemically. They are stable in the p_H range which is tolerated by the eye and seem unaffected by light or aging. Aqueous solutions are compatible with the drugs commonly used in ophthalmology. Solutions containing only pure cellulose do not support bacterial or fungous growth.

Methyl cellulose in a dry state occurs as fluffy, white, corklike fibers. It has the disadvantage that preparation of a solution is rather complex. The dry material must be boiled with approximately one half of the required volume of water, then stirred while cooling to a temperature of 5 to 10 C. When used as a substitute for tears in cases of keratoconjunctivitis sicca, a 0.5 to 1.0 per cent solution of 4,000 centipoise type of methyl cellulose containing 0.9 per cent sodium chloride has proved more satisfactory than other types of artificial tears. Unlike the commonly used oily vehicles of high viscosity, solutions of methyl cellulose mix well with secretions and spread smoothly throughout the conjunctival sac. Conjunctival irritation is reduced by the emollient properties of the colloid. If there is secondary infection, such as commonly occurs in established cases of keratoconjunctivitis, bacteriostatic agents may be added.

The corneal epithelium seems like a child in its reactions; i. e., it is easily hurt but heals quickly without scar formation. Like a child with whom the rod has been spared, too gentle treatment of epithelial conditions, such as herpes simplex or recurrent erosion, results in recurrence or progression. Also like a child, the epithelium has a high metabolic rate and is sensitive to nutritional disturbances. For example, vitamin A deficiency results in a characteristic hyperplasia and metaplasia. The epithelium becomes thickened; the rate of desquamation is increased, and there is a tendency toward keratinization. Lee and Hart [5] demonstrated that the oxygen consumption of the epithelium of vitamin A–deficient animals is greatly increased. In contrast, they observed that riboflavin deficiency results in diminished metabolic activity. A superficial punctate type of keratitis results in experimental riboflavin deficiency, and there is delayed healing of abrasions before corneal vascularization begins. It is likely that neovascularization of the cornea, which has been reported to be the earliest sign of clinical

5. Lee, O. S., Jr., and Hart, W. M.: Respiration or Metabolism of Cornea: Metabolism of Cornea; Studies on Oxygen Consumption of Corneas of Riboflavin and Vitamin-A-Deficient Rats, Am. J. Ophth. **27**:488 (May) 1944.

riboflavin deficiencies, is secondary to these epithelial changes. Certainly, marginal neovascularization of the cornea has not been a consistent clinical finding.

The corneal epithelium regenerates at a remarkable rate, and two mechanisms are involved. Small defects in the epithelium are filled by migrations of the deeper layers of the neighboring epithelial cells, a process which has been photographed by Friedenwald. In large defects, cell division and multiplication also occur, a process which may be studied by observing mitotic activity. It has been stressed that the epithelium may even grow over necrotic corneal stroma, such as the edge of a corneal ulcer. Despite this rapid and vigorous regeneration, it is likely that the epithelium requires fairly normal underlying stroma for permanent maintenance of its health. This fact is best seen in the healing of corneal burns, particularly those occurring from steam. In this type of burn, dense, avascular scar formation occurs in the superficial stroma. The epithelium will heal to the edge of the eschar, but will either progress no farther or form an unstable bleb over the scar. If the eschar is dissected away under the surgical microscope, the defect rapidly epithelizes.

Regeneration of normal corneal epithelium occurs at a rate so rapid that the epithelial stimulants have not been of clinical value. On the other hand, a number of compounds, notably the local anesthetics, significantly impair the process of regeneration. Friedenwald and Buschke,[6] in experiments on the excised rat cornea, observed that tetracaine impaired regeneration. Smelzer and Ozanics[7] made a similar laboratory observation with other anesthetics but noted that the impairment of regeneration was not directly proportional to the degree of anesthesia. Their work offers the hope that local anesthetics may be developed which do not impair epithelial growth. My studies with several large series of new synthetic anesthetics have not revealed such a compound.

It is necessary to use local anesthesia for removal of corneal foreign bodies and repair of lacerations, but repeated or prolonged use of these drugs impairs healing of epithelial defects. For example, 3 men working in a tightly closed room received bilateral injury to the corneal epithelium from escaping ammonia fumes. Tetracaine ointment was injected into the lacrimal canaliculi and placed in the conjunctival sac of the least seriously injured eye of each of the 3 patients. The treated eyes were more comfortable during the first few hours, but recovery

6. Friedenwald, J. S., and Buschke, W.: Mitotic and Wound-Healing Activities of Corneal Epithelium, Arch. Ophth. **32**:410 (Nov.) 1944.

7. Smelzer, G. K., and Ozanics, V.: Effect of Local Anesthetics on Cell Division and Migration Following Thermal Burns of Cornea, Arch. Ophth. **34**: 271 (Oct.) 1945.

was delayed. The untreated eyes completely healed in an average of eighteen hours, but the tetracaine-treated eyes remained irritable and stained with fluorescin until twenty-four to forty-eight hours after the injury.

It has been known for many years that epithelial defects heal most rapidly when the eye is bandaged. It has been assumed that pressure and immobilization of the eye are the important factors in the accelerated epithelial regeneration, but it is likely that elevation of the temperature of the conjunctival sac by bandaging also contributes to more rapid healing. The temperature of the corneal surface is normally maintained several degrees below body temperature by exposure and evaporation. A heavy bandage effectively raises the temperature by blocking this loss of heat and producing active hyperemia in the lids.

Friedenwald and Buschke,[8] working with excised rat corneas, found that epithelial regeneration has a high temperature coefficient. We have confirmed this observation with in vivo experiments on the rabbit. Fine thermocouples incorporated in a double contact lens were placed over the cornea. Then the temperature of the inner lens and cornea was varied by irrigating the space between the two lenses with solutions of varying temperatures. Changes in temperature of a few degrees (C.) appreciably affected the rate of healing of the corneal defect. In view of this fact, local applications of heat, as well as immobilization, seem a logical procedure to accelerate healing of injuries to the epithelium of the cornea.

The exact mechanism by which certain drugs produce anesthesia when applied locally to cells has not been fully established; however, some of the factors which influence the penetration of local anesthetics into the corneal epithelium have been determined. The physical properties of the various local anesthetics greatly influence their penetrability into the cornea and thereby their clinical effectiveness. In 1940, White and I[9] determined by quantitative chemical analyses the penetrability into the cornea of a group of local anesthetics of the para-aminobenzoic acid ester series. We observed that tetracaine, a highly surface-active compound, reached a much higher concentration in the corneal epithelium than procaine, a chemically related compound of relatively low surface activity. Butacaine (butyn®), a compound of intermediate surface activity, was less concentrated in the epithelium than tetracaine but considerably more concentrated than procaine. It is possible to

8. Friedenwald, J. S., and Buschke, W.: Influence of Some Experimental Variables on the Epithelial Movements in Healing of Corneal Wounds, J. Cell. & Comp. Physiol. **23**:95 (April) 1944.

9. Swan, K. C., and White, N. G.: Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043 (Sept.) 1942.

correlate penetrability with effectiveness of the compound when applied topically to the epithelium (fig. 3). In general, highly surface-active compounds, like tetracaine, are effective when applied topically, whereas surface-inactive compounds, such as procaine, are effective only when injected under the epithelial barrier.

Factors other than surface activity influence corneal penetrability of anesthetics. There are a number of topically effective local anesthetics which are not highly surface active, but the compounds of high surface activity are notable for the rapidity of their action. For example, the corneal anesthesia induced by 0.5 per cent tetracaine hydrochloride becomes evident in a matter of seconds. Also, highly surface-active anesthetics have a greater miscibility with the conjunctival secretions and greater wetting power; consequently, they spread more evenly throughout the conjunctival sac. It is common experience to instill

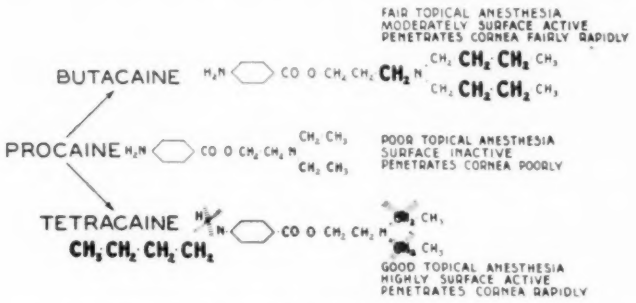

Fig. 3.—Comparison of butacaine (butyn®), procaine and tetracaine with respect to penetrability and effectiveness.

a relatively surface-inactive local anesthetic into the conjunctival sac and then to discover, when the speculum is placed, that the fornices have not been anesthetized. This is least apt to occur when highly surface-active anesthetics are used. Finally, all highly surface-active compounds have antiseptic power, and a bacterial action is highly desirable in a topical anesthetic used for tonometry or for the removal of infected foreign bodies embedded in the epithelium.

It has been known since the discovery of cocaine that local anesthetics have a deleterious effect on the epithelium. These effects are characterized by drying and roughening of the epithelial surface and by increased permeability of the epithelium to other drugs. Drying of the epithelium is related, at least in part, to impairment of several protective reflexes; e. g., mucous secretion of the goblet cells and lacrimal flow are diminished, and there is decreased winking. The vehicle in which the anesthetic is administered also has some influence.

Holt and Cogan [10] reported that epithelial changes are largely eliminated if hypertonic or isotonic solutions of the local anesthetic are used. There is no doubt that the control of osmotic pressure of the fluid in the conjunctival sac and the prevention of drying greatly reduce the gross disturbances of the epithelium associated with topical application of local anesthetics; nevertheless, some alteration in the physicochemical state of the cells occurs from topical anesthesia, for increased permeability of the cornea induced with cocaine is independent of the degree of anesthesia and occurs even if isotonic, or even hypertonic, solutions are used.

The epithelium is a highly sensitive structure. This sensitivity limits types and concentration of drugs which may be applied topically; consequently, the factors which make drug solutions irritating have received much consideration. In the past, emphasis has been placed on the physical properties of the drug vehicle. For example, great stress has been placed on making ophthalmic solutions isotonic with the tissue fluids. Most of the commonly used drug solutions are hypotonic, but, owing to the protective and diluent action of the conjunctival secretion and the precorneal film, even highly hypotonic solutions do not produce a discomforting sensation or biomicroscopic alterations in the corneal epithelium unless they are instilled repeatedly or used for irrigation. For example, a single drop of distilled water is well tolerated, although irrigation results in severe epithelial changes. The addition of nonmedicament solutes to make ordinary eye drops isotonic is, therefore, unnecessary and increases the danger of the pharmacist's making an error in preparation of the prescription. On the other hand, strongly hypertonic solutions are rather irritating and should be avoided if possible. It is interesting to note that the pain produced by such solutions is influenced little by topical anesthesia.

The acidity and alkalinity of ophthalmic drug solutions has also received considerable attention as a source of irritation. In general, solutions with a p_H of 6 to 8 are less irritating than those outside that range; but whether a more highly acid or alkaline vehicle is irritating depends a good deal on the concentration of the drug and its buffer power. For example, the buffering of a dilute solution of alkaloids, such as 0.2 per cent solution of scopolamine hydrobromide, is unnecessary even though the p_H of such a solution may be quite low, because the acidity of these weak preparations is almost instantly neutralized by the conjunctival secretions. On the other hand, buffering of concentrated solutions, such as 5 per cent homatropine hydrobromide, is

10. Holt, M., and Cogan, D. G.: Cornea: Permeability of Excised Cornea to Ions, as Determined by Measurements of Impedance, Arch. Ophth. **35**:292 (March) 1946.

desirable. Such solutions become quite acid with deterioration and are sufficiently concentrated that rapid neutralization by the conjunctival secretions does not occur. It is our policy to buffer this particular preparation to p_H 6, rather than to one on the alkaline side, so that it is retained in the stable salt form.

Surface activity influences the tolerance of the epithelium toward the drug. Dilute solutions of wetting agents [11] are well tolerated, and such agents are useful in the treatment of external inflammations. They have antiseptic action and detergent powers, which facilitate removal of infected discharge from the conjunctival sac and lid margins; however, the low toxicity of these compounds has been unduly stressed by pharmaceutical manufacturers. Many wetting agents have produced

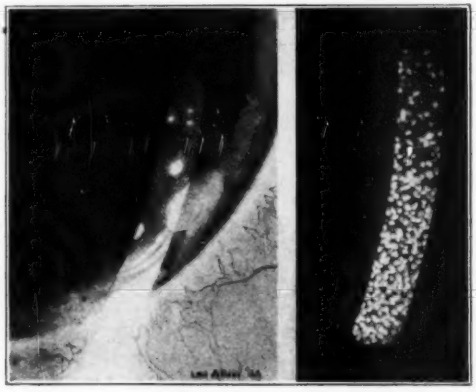

Fig. 4.—Superficial punctate lesions of epithelium produced by wetting agent.

less cellular damage than agents with comparable degrees of antibacterial action, but they are capable of producing injury to the epithelial tissues.[12] Repeated instillations of even dilute solutions of wetting agents into the conjunctival sac result in a superficial punctate type of keratitis, differing from the changes which occur in the epithelium as a result of local anesthetics or hypotonic solutions (fig. 4). The influence of surface activity on conjunctival irritation is well demonstrated with salts of dibutoline (salts of dibutyl carbamate of dimethyl-β-hydroxyethylammonium). This is a new compound which has

11. These compounds are spoken of as wetting agents because they greatly lower the surface tension of water and thereby facilitate wetting of water-insoluble substances.

12. Swan, K. C.: Reactivity of the Ocular Tissues to Wetting Agents, Am. J. Ophth. **27**:1118 (Oct.) 1944.

an atropine-like action on the intraocular muscles.[13] Halide salts were initially prepared but were found to be poorly tolerated by the conjunctiva. The sulfate, which was less highly ionized, and therefore less surface active in solution, produced much less irritation of the conjunctiva [14] (table).

In general, vehicles containing an emollient substance, such as albumin or methyl cellulose, are better tolerated by the cornea than a simple aqueous solution, because they do not reduce the normal emollient substances of the precorneal film. On the other hand, vehicles such as oils do not mix readily with the conjunctival secretions and may produce mechanical irritation despite lubricant qualities. Other factors influence irritation of the epithelium by medicaments which are not understood. For example, in the synthesis of new atropine-like drugs, my associates and I observed that carbamic acid esters of ethyl alcohol containing a quarternary ammonium group were less irritating than the corresponding tertiary amines.[14]

Surface Activities and Effects of Salts of Dibutoline on the Conjunctiva

Dibutoline Salt	Surface Tension of 5% Aqueous Solution, Dynes/per Cm. at 25 C.	Conjunctival Irritation from Single Instillations of 5% Solutions
Iodide	36	++
Chloride	39	++
Methyl sulfate	45	+
Sulfate	47	±

Knowledge of the permeability characteristics of the epithelium is important because the epithelium is the major barrier to penetration of drugs into the cornea. Also, such knowledge is essential to the clinical management of edema of the epithelium and vascular keratitis. Until recent years it has been assumed that the cornea, contrary to all physical laws, was impervious to water, although it permitted a transfer of other compounds. This false hypothesis was based on the observation that edema of the cornea followed any physical damage to the epithelium or endothelium. In 1942, White and I [9] reported that, in general, epithelium was relatively impermeable to highly polar compounds. More specifically, Cogan and Kinsey [15] demonstrated that the epithelium and endothelium of the cornea were permeable to water and relatively impermeable to sodium and chlorides. They concluded that, because

13. Swan, K. C., and White, N. G.: Dibutoline Sulfate, Arch. Ophth. **33**:16 (Jan.) 1945.

14. Swan, K. C., and White, N. G.: Choline Esters with Mydriatic and Cycloplegic Action, Am. J. Ophth. **27**:933 (Sept.) 1944.

15. Cogan, D. G., and Kinsey, V. E.: Physiologic Studies on the Cornea, Science **95**:607 (June 12) 1942.

of this relative impermeability of the epithelium and endothelium to sodium chloride, an osmotic balance exists between the corneal stroma, on the one hand, and the aqueous and external secretions, on the other. They postulated that the corneal stroma exists in a state of detergescence, which is associated with normal optical clarity of the stroma.[16] They demonstrated that if the corneal stroma is maintained in a state of hypertonicity as contrasted with the solutions external to the epithelium bedewing of the epithelium, and an even experimental type of vascular keratitis, may result and that the process may be reversed by making the external fluids hypertonic or by administration of a hygroscopic substance, such as glycerin. This observation is important to clinical ophthalmology. For example, in patients with acute congestive glaucoma study of the internal eye by biomicroscopy and ophthalmoscopy is greatly impaired by the corneal bedewing. As reported by Cogan, the topical administration of glycerin effects transitory clearing of a bedewed cornea, thus permitting a more adequate examination.

Considering that bedewing of the cornea is dependent on the epithelium's acting as a semipermeable membrane, any physical disruption of such a membrane or chemical alteration of its permeability tends to decrease the edema. For example, corneal bedewing in glaucoma can be reduced by administration of a local anesthetic and mechanical massage of the epithelium with the rounded tip of a glass rod. The most effective and prolonged clearing results from combining this method with the administration of glycerin. For example, a drop of 0.5 per cent tetracaine hydrochloride is instilled over the cornea. With the patient in a reclining position, the lids are separated and a drop of glycerin is instilled. The epithelium is then gently massaged through the glycerin. An immediate and spectacular clearing of corneal bedewing generally occurs, although a clearing of gross bullous keratitis is not to be expected.

Bowman's membrane and the corneal stroma differ diametrically from the corneal epithelium. Metabolic activity is relatively low but increases with vascularity and increased cellularity, such as accompanies damage to the cornea from prolonged riboflavin deficiency or any inflammatory process. The passage of substances through the corneal stroma simulates the diffusion in a simple aqueous solution. It was known in the nineteenth century that diffusion readily occurs from the blood vessels in the corneal limbus toward the center of the cornea. A classic experiment was to place particles of iron into corneal stroma and to study the staining of the cornea which took place when potassium ferrocyanide was injected intravenously. The staining of the cornea

16. Cogan, D. G.: Glycerin in Cornea: Clearing of Edematous Corneas by Glycerine, Am. J. Ophth. **26**:551 (May) 1943.

due to the formation of prussian blue begins at the periphery earlier than at the center, indicating that the ferrocyanide reached the cornea via the limbic plexus. In recent experiments in our laboratories Taylor and I have injected dibutoline and other drugs into the corneal stroma with a fine needle under high magnification and have found rapid lateral spread, as well as penetration into the aqueous.[17] Limbic injections also spread into the cornea.

Bowman's membrane is a unique layer with many of the staining characteristics of the stroma. It is much more highly permeable to most substances than is the epithelium. Most tinctures and such acid caustics as trichloroacetic acid and phenol are tolerated well, but degenerative conditions develop slowly after prolonged or intense chemical or infectious inflammations of the anterior segment. For example, deposition of calcium phosphate long after an injury is a commonly observed clinical phenomenon. Lowenstein expressed the belief that this deposition occurs from altered permeability of the membrane and increased alkalinity by loss of carbon dioxide.[18]

The war has resulted in renewed interest in the controversy over the nature and management of acid and alkali burns to the cornea. It has long been known that acid burns may produce immediate severe damage but that the burn is limited to the area of contact. This type of reaction is to be expected, for acids coagulate protein and therefore tend to be fixed by the process. On the other hand, alkalis tend to dissolve protein and are less effectively buffered by it than are acids; consequently, alkali burns to the cornea would be expected to produce progressive injury. Formerly, it was thought that the damage to the stroma from the alkalis was delayed reaction, but experimental data indicate that the process, rather than being a delayed response, is one of progressively deeper damage as the alkali penetrates from the epithelium into the corneal stroma. For this reason, immediate removal of irreparably damaged epithelium would seem the logical emergency procedure to prevent spread of alkali to the epithelial layers and has come into general use. Whether denudation is performed in individual cases seems a matter of clinical judgment, but immediate and prolonged irrigation of the conjunctival sac with isotonic solution of sodium chloride is imperative in all cases of alkali burns. Attempted neutralization of acid or alkali in the cornea with buffer solutions has been disappointing in my experience. Eyes have been lost from delay in treatment resulting from the preparation of such a solution. In a recent medicolegal case, the physician delayed irrigation of the con-

17. Taylor, J., and Swan, K. C.: Intracorneal Permeability: II. Factors Affecting Distribution of Drugs in the Corneal Stroma, to be published.

18. Lowenstein, A.: Contribution to Pathology of Bowman's Membrane, Brit. J. Ophth. **30**:317 (June) 1946.

junctival sac for fifteen minutes while he prepared and sterilized an isotonic buffer solution. The eye was lost, and the physician was subjected to considerable public criticism.

An interesting and important toxic reaction of the corneal stroma occurs in relation to the breakdown of iron foreign bodies. If metallic iron is embedded in the corneal stroma, it breaks down into ionic form, which diffuses into and reacts with the surrounding tissue to form conspicuous brown rust rings. If the piece of metal is removed, the epithelium often closes over the rust ring, resulting in a permanent corneal opacity. No further symptoms may result if the ring is small, but with large rings necrosis of the iron-stained tissue may occur in one to three days, with resultant return of ocular irritation. At this stage the rust ring can readily be lifted out with a dull spud or may actually extrude itself. On the other hand, freshly stained collagenous corneal tissue is tough and requires sharp dissection or curettage. Therefore, in an individual case it is a matter of clinical judgment whether rust rings and tough viable tissue should be taken out immediately after the foreign body is removed or left, with the hope that healing will occur. If extensive deep instrumentation is necessary to excise or curette a fresh, large rust ring, it may be safer and may produce less scar tissue if the physician waits until necrosis makes removal of the damaged tissue easy. Eyes have been perforated by ophthalmologists attempting to remove rust rings with dental burrs.

Solutes diffuse readily out of the corneal stroma, but suspensions of relatively insoluble materials, such as the commonly used silver proteinate preparations, may be retained in the corneal stroma. When such preparations are administered in the presence of a deep corneal laceration, the epithelium and later scar tissue may grow over the suspended material, to form an accidental tattoo. Inert materials may safely be used in tattooing of the cornea, but substances like the silver proteinates break down slowly, with disastrous effects on vision. The delayed deterioration of vision results from concentration of the heavy metal in Descemet's membrane, with the formation of an irreversible flocculent gray opacity. The accompanying illustration (fig. 5*A*), shows the typical appearance of a silver proteinate, mild silver protein U. S. P., retained in the corneal stroma. Months after administration of the preparation to a corneal laceration, the brown appearance of the unchanged suspension may still be seen in the center, but around the edges a grayish green discoloration is evident grossly. Slit lamp biomicroscopy reveals a typical grayish green discoloration of Descemet's membrane. Treatment in such cases involves excision of the involved stroma to prevent further damage to Descemet's membrane. Silver staining of Descemet's membrane also occurs with prolonged administration of silver preparations to the conjunctival

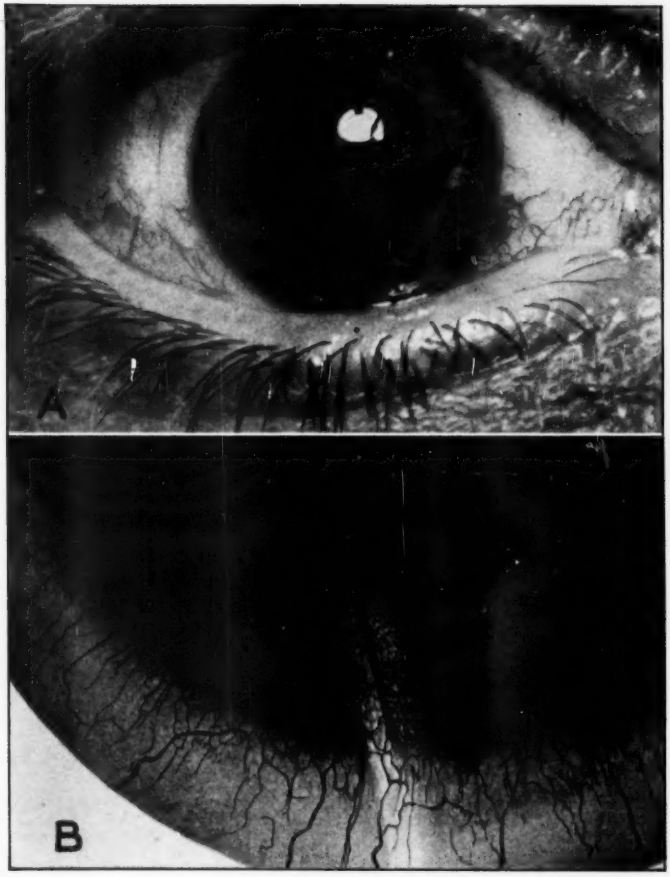

Fig. 5.—*A*, accidental tattoo of cornea with mild silver protein U. S. P.; *B*, copper staining of Descemet's membrane.

sac (fig. 5 *B*). The majority of patients with gross argyria of the conjunctiva also have biomicroscopic evidence of staining in the peripheral regions of Descemet's membrane. This membrane reacts with other heavy metals. Discoloration was recently observed in that part of the membrane over which a copper foreign body had been embedded in the stroma for months. The process was checked by removal of the foreign body. Von Sallmann [19] and Allen and I (fig. 5 *B*) noted changes in Descemet's membrane in patients with trachoma who had received extensive and prolonged topical applications of copper sulfate, and Abramowicz [20] has recently reported a discoloration of Descemet's membrane from the prolonged application of mercurial ointment.

The endothelium is exceedingly sensitive to injury, both chemical and physical. All ophthalmic surgeons are aware that the slightest trauma to the posterior surface of the cornea is followed by edema of the overlying stroma. Even the vitreous pushed against the posterior corneal surface produces a disturbance of the endothelium and edema of the deeper corneal stroma overlying the point of contact. If the vitreous has ruptured and is adherent to the posterior corneal surface, as may occur after a cataract extraction, the stroma is edematous over the area of contact and bedewing of the epithelium results. Some toxins, such as dimethyl sulfate, produce endothelial damage even when administered systemically.

The endothelium is so sensitive to chemical and physical injury that great care must be observed in the selection and preparation of solutions used in the irrigation of the anterior chamber. Several years ago, when wetting agents were introduced as antiseptics of extremely low toxicity, it was suggested that addition of these agents to saline solution would reduce the danger of intraocular infection from irrigation of the anterior chamber after cataract extraction. We found experimentally that even minute concentrations of these agents produced severe endothelial damage and subsequent corneal edema (fig. 6).

The use of mercurial antiseptics is also impractical. Recently, antibiotics have been added to irrigating solutions. Ophthalmologists commonly use concentrations of penicillin up to 5,000 units per cubic centimeter in the anterior chamber. Such high concentrations are necessary and carry the risk of chemical injury. No report of injections of penicillin into the anterior chamber in hypersensitive patients has appeared, but allergic reactions to penicillin are reported with increased frequency. It would seem unwise to use antibiotics routinely in irrigating fluids until the nature of intraocular reactions in hyper-

19. von Sallmann, L.: Ueber Hornhautverkupferung nach therapeutischer Anwendung von Kupferpräparaten, Ztschr. f. Augenh. **57**:373, 1925.

20. Abramowicz, I.: Mercury Staining of Cornea: Deposition of Mercury in Eye, Brit. J. Ophth. **30**:696 (Nov.) 1946.

sensitive persons is established. This should not prevent the ophthalmologist from injecting the antibiotic into the anterior chamber in cases of serious intraocular infections due to susceptible organisms.

It has become an almost standard procedure in this country to irrigate the anterior chamber with one-half strength isotonic solution of sodium chloride, rather than with 0.9 per cent sodium chloride. It is possible that in the presence of lens material in the anterior chamber, such as occurs in extracapsular cataract extraction or in the presence of blood, hypotonic saline solution might be superior, but in the rabbit one finds solutions isotonic with the aqueous to be best tolerated.

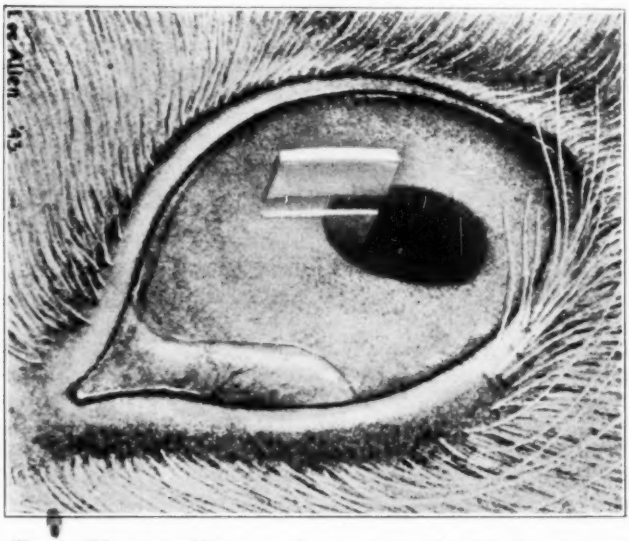

Fig. 6.—Edema of rabbit cornea fourteen hours after injection of a wetting agent into anterior chamber.

Prolonged irrigation with markedly hypotonic solutions definitely damages the endothelium, as evidenced by clouding of the overlying stroma. These changes occur almost immediately after the chamber is irrigated with concentrations of 0.2 per cent sodium chloride or less.

On the basis of knowledge of the permeability characteristics of the individual corneal layers and of anatomic differences between different parts of the cornea, a number of principles pertaining to the clinical administration of drugs by topical application become evident.

It was established years ago that the conjunctiva is not impermeable, but drugs penetrating this membrane pass largely into the general

circulation. Therefore, drugs instilled into the conjunctival sac must enter the anterior chamber mainly via the cornea. The quantity of a given drug penetrating the cornea increases with the area of the cornea in contact with the drug solution and with the period of contact; therefore the first principle of administering a drug for its intraocular effects is to bring the drug vehicle into contact with the cornea and to maintain that contact for the longest possible time. To do so, several physiologic facts must be considered: (1) The normal flow of tears is down and toward the internal canthus; (2) emptying of the conjunctival sac is accelerated by winking and is delayed by closure of the lids; (3) a liquid introduced into the conjunctival sac remains in concentrated form in the lower fornix longer than in other parts of the conjunctival sac, and (4) the cornea is rotated upward with closure of the lids. Therefore, to instil a drug solution for maximal intraocular effects, the upper lids should be elevated and the eye drops instilled to flow down the cornea into the lower fornix. The patient is then advised to close the eye to keep the solution in the conjunctival sac and to look down to bring the cornea in contact with the reservoir of drug in the lower fornix. Pressure on the inner canthus, properly applied, is also of value in keeping the drug solution in the conjunctival sac.

To maintain a given drug in contact with the cornea, it is desirable to administer the drug in vehicles of high viscosity. Oils and ointments remain longer in the conjunctival sac than simple aqueous solutions, but do not mix well with the conjunctival secretions. Several new agents of high viscosity and of greater miscibility have been developed. The most important of these, methyl cellulose, has already been discussed as a substitute for lacrimal secretion. A 2 per cent solution provides a highly efficient vehicle for administering suspensions of water-insoluble drugs, such as sulfamerazine. It has advantages over emulsions and ointments, being nongreasy and mixing readily with the conjunctival secretions. Finally, the colloid is completely neutral and almost chemically inert and is not absorbed by the conjunctiva. No evidences of hypersensitivity have been observed.

The use of wetting agents as vehicles to enhance the absorption of drugs has already been mentioned in relation to irritation of the epithelium. In 1940, O'Brien and I [21] reported that when a wetting agent was added to the solution carbaminoylcholine was more effective in treatment of glaucoma. This observation that surface-active agents enhanced penetration of drugs into the tissues has been confirmed, and wetting agents are now commonly incorporated in dermatologic, as well as in ophthalmic, prescriptions to enhance absorption of other

21. O'Brien, C. S., and Swan, K. C.: Carbaminoylcholine Chloride in the Treatment of Glaucoma Simplex, Arch. Ophth. **27**:253 (Feb.) 1942.

drugs and to exert their antibacterial action. Wetting agents enhance the clinical effectiveness of drugs administered for intraocular purposes by at least two mechanisms: They improve contact of the drug solution with the corneal epithelium by increased miscibility of the solution with the precorneal film, and, secondly, they directly influence the permeability characteristics of the epithelium.

The degree to which wetting agents increase penetrability of a compound depends on the penetrability of that compound, particularly

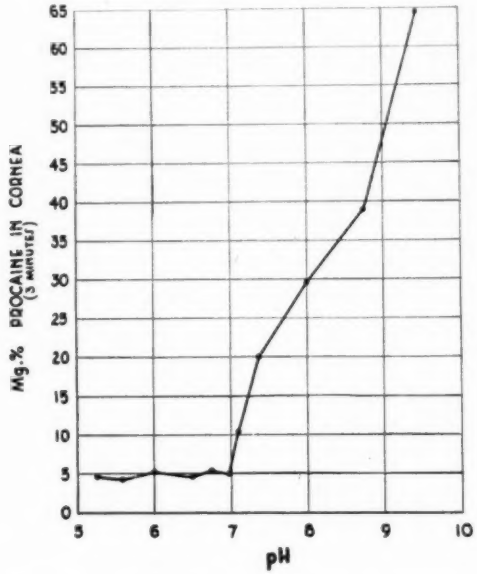

Fig. 7.—Effect of p_H of the solution on the rate of penetration of procaine hydrochloride into the cornea. The solution of procaine contained 100 mg. per hundred cubic centimeters.

into the cornea, from aqueous solutions. The penetrability of poorly penetrating compounds, such as penicillin and carbaminoylcholine, is enhanced to a greater degree than is that of the alkaloids. In clinical practice, the increased effectiveness of aqueous vehicles containing wetting agents is masked by the fact that a much smaller dose of the drug is actually given if a standard eye dropper is used.

Considerable emphasis has been placed on the p_H of drug vehicles in relation to corneal penetration. It has been emphasized that certain drugs, particularly alkaloids and local anesthetics, penetrate the cornea

much more rapidly in alkaline than in acid solution. For example, White and I[9] found that procaine penetrated much more rapidly in alkaline than in acid solution (fig. 7). This is true because in alkaline solutions these drugs exist principally as free bases. The free bases have a much higher affinity for the lipid constituents of the corneal epithelium than for the aqueous drug vehicle; consequently, they pass readily into the cornea. Unfortunately, use of alkaline solutions of the alkaloids in anesthetics is impractical for clinical purposes because the free bases are relatively insoluble in water and are unstable. Control of the p_H of the vehicle is therefore not of value in enhancing corneal penetration but is of importance only in reducing the irritating action of concentrated acid or alkaline drug solutions. When it is desirable to buffer solutions of alkaloids, a p_H of between 6 and 7 is selected. Otherwise, the alkaloids will not be retained in the stable salt form.

On theoretic grounds, the osmotic pressure of drug vehicles has also received considerable emphasis as a factor effecting penetration of drugs into the cornea, but experimental evidence indicates that it has little influence unless the vehicle is either so hypotonic or so hypertonic that the epithelial barrier is reduced by injury.

There is another factor of much greater importance than the acidity, alkalinity or tonicity of a drug vehicle. For decades it was assumed that all drugs penetrated the eyeball equally well from aqueous solutions by the simple process of diffusion. This assumption is erroneous. Even compounds which are chemically related vary greatly in the rapidity with which they penetrate the cornea. Penetration of drugs into the eye is largely dependent on the relative physical properties of the drug and the vehicle.[9] To be administered with maximal effectiveness, a drug should be given in a vehicle for which it has less affinity than for the cornea and the conjunctival epithelium. This rule depends on the fact that the distribution of the given drug between the drug vehicle and the cornea bears the same relation as the distribution of a solute between two immiscible solvents (fig. 8). For example, if a drug having a high affinity for oil is added to a mixture of oil and water, it will become concentrated in the oil and little will enter the water, whereas a highly water-soluble drug will become concentrated in the water and little will enter the oil. The epithelium of the cornea and the conjunctiva contain both water and lipid elements. If carbaminoylcholine or penicillin sodium, which have a very high affinity for water, are instilled into the conjunctival sac in simple aqueous solutions, they will remain in the water, and little will pass into the corneal epithelium.

The general rule, then, is that highly water-soluble drugs should be administered in an oil vehicle or in some other type for which they

have low solubility. On the other hand, compounds which have a high solubility for oils and fats should be administered in water, for which they have a relatively lower affinity than for the corneal epithelium. Drugs which are intermediate in their solubility, such as atropine and scopolamine, are absorbed from almost any type of vehicle, but the effectiveness of such drugs as carbaminoylcholine, sodium penicillin and the sulfonamide series may be increased as much as one hundred by the selection of a proper vehicle for administration.

Carbaminoylcholine provides a good example of the application of this simple law of "relative affinities." This compound was introduced in the treatment of glaucoma more than a decade ago, but it

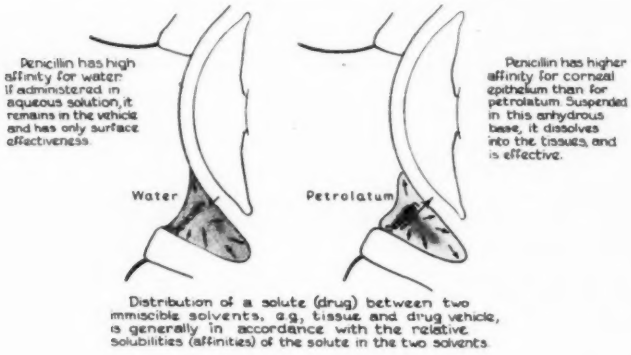
Penicillin has high affinity for water. If administered in aqueous solution, it remains in the vehicle and has only surface effectiveness.
Water
Petrolatum
Penicillin has higher affinity for corneal epithelium than for petrolatum. Suspended in this anhydrous base, it dissolves into the tissues, and is effective.
Distribution of a solute (drug) between two immiscible solvents, e.g., tissue and drug vehicle, is generally in accordance with the relative solubilities (affinities) of the solute in the two solvents.

Fig. 8.—Law of relative affinities.

was not recognized that the drug was poorly and inconsistently absorbed from simple aqueous solutions; consequently, controversial reports appeared in the literature in regard to its duration of action and degree of potency. In 1939 I discovered that the effectiveness of carbaminoylcholine could be increased as much as two hundred times by disturbance of the epithelium. In 1942 Dr. O'Brien and I reported that the effects of carbaminoylcholine in cases of glaucoma simplex were more intense and more prolonged than equal doses of pilocarpine, provided precautions were taken to insure its absorption. A suspension of the dry powder of this hygroscopic drug in liquid petrolatum U. S. P. is many times as effective as equal concentrations dissolved in water.[22]

22. Swan, K. C.: Carbaminoylcholine Chloride in Petrolatum, Arch. Ophth. **30**:591 (Nov.) 1943.

The local use of penicillin in the conjunctival sac provides another example of the great importance of the law of relative affinities. Salts of penicillin are commonly prescribed in aqueous solutions. If the corneal epithelium is intact, such solutions have only a surface action unless administered by constant irrigation. The relative ineffectiveness of single instillations of aqueous solutions of penicillin was recognized early, and a number of irrigating eye cups were devised for the purpose of constant irrigation of the conjunctival sac. Overlooked was the fact that penicillin salts are hygroscopic and therefore stay in the aqueous solution rather than penetrate the lipid-protein surfaces of the epithelial cells. In contrast, penicillin salts have a higher affinity for the cells than for an anhydrous ointment base; therefore dry suspensions of penicillin in anhydrous ointment bases are highly effective. Much higher concentrations of the drug can be isolated from a single application of such ointment than can be obtained by fifteen minutes of bathing the cornea with an aqueous solution of equal concentration. Also, penicillin is more stable as a dry suspension in an anhydrous base than as dissolved in aqueous solution. This fact has been recognized by pharmaceutical manufacturers; consequently, anhydrous ointments containing penicillin are commercially available.

As a rule, a suspension of a drug in finely powdered form is most effective for topical administration. In such forms the suspended drug passes from the vehicle directly into concentrated solution in the precorneal film or the epithelial cells. It is obvious that drugs which are caustics or highly irritating in concentrated form cannot be administered by this method, but most of the ophthalmic drugs can be safely administered in suspension—for example, a suspension of sodium penicillin in petrolatum. Most pharmaceutical manufacturers have not recognized the effectiveness of suspensions. On the contrary, they have gone to great effort to find vehicle bases in which compounds like the free sulfonamide drugs are readily soluble. None of these vehicles is as effective as suspensions of the free sulfonamide compounds in a jelly.

It has already been stated that the corneal epithelium is the most important barrier to the penetration of drugs from the conjunctival sac into the anterior chamber. Physical injury to this barrier whether by trauma, such as that produced by massage of the cornea through the lids, or by a chemical agent, such as an anesthetic, results in an increased permeability of the cornea to drugs. The increased permeability again varies in accordance with the law of relative affinities, but in a different manner than when the epithelium is intact. Highly water-soluble drugs, such as methacholine (mecholyl ®) chloride, most epinephrine salts and penicillin, when administered in aqueous solution

penetrate the epithelium poorly. Even simple massage of the cornea through the lids greatly increases corneal penetration of these drugs. This is important clinically, not only because of the increased ocular action but in relation to systemic toxic effects. For example, 1 drop of 1 per cent epinephrine hydrochloride instilled into a normal conjunctival sac will rarely produce systemic symptoms because from aqueous solutions it penetrates the normal epithelium more slowly than it is broken down in the body. However, if the permeability of the conjunctival epithelium has been greatly increased by instillation of a local anesthetic or by tonometry, sufficient epinephrine may be absorbed into the systemic circulation to effect a dangerous rise in blood pressure. Toxic systemic reactions to carbaminoylcholine may occur in similar circumstances. The corneal penetration of less hydrophilic compounds, such as atropine, is accelerated by removal of the epithelial barrier, but not to the same extent as with hydrophilic compounds like penicillin.

On occasion, emergencies arise in which it is necessary to obtain a high concentration of a drug in the cornea or the anterior chamber within a matter of minutes. The emergency might be corneal abscess, a rapidly advancing infected ulcer, an overwhelming infection of the anterior chamber or acute congestive glaucoma. In these circumstances, simple applications of drugs may be inadequate even when combined with systemic therapy. The ophthalmologist must then depend on so-called iontophoresis to obtain rapidly a high concentration of drugs in the tissues. Most ophthalmic drugs are electrolytes; consequently, they may be driven into the tissue by means of a weak galvanic current. For example, when a direct electric current is run through a solution containing a drug such as atropine hydrobromide, ionization occurs. The atropine ion, being positively charged, moves away from the positive pole toward the negative pole, whereas, if the solution contains sodium sufamerazine, the sulfamerazine ion, carrying a negative charge, moves away from the negative toward the positive pole. Similar effects occur in the tissues; for example, if the negative pole is held by the hand and the positive pole applied to the eye through solution containing atropine sulfate, the current will drive greater quantities of atropine into the eye than would be possible by simple instillation. Von Sallmann found that the amounts of atropine which could be introduced into the aqueous humor of rabbits by corneal iontophoresis were six to nine times as great as those introduced into the aqueous humor by subconjunctival injection or by a corneal bath applied for the same period.[23] Von Sallmann used also iontophoresis to introduce sulfona-

23. von Sallmann, L.: Iontophoretic Introduction of Atropine and Scopolamine into the Rabbit Eye, Arch. Ophth. **29**:711 (May) 1943.

mide drugs and penicillin into the eye. In our experience, it has seemed the most effective method of obtaining therapeutic concentrations of drugs in the cornea and the anterior chamber.

Rather than use a solid electrode in a glass cup to apply drugs to the cornea by iontophoresis, the drug, e. g., 1 per cent sodium sulfamerazine, may be dissolved in a 4 per cent aqueous solution of the 4,000 centipoise type of methyl cellulose. The solution is placed in a glass syringe with a metal plunger connected to a galvanic current with variable resistance and voltage. The lids are separated and a drop of the highly viscous solution suspended from the tip of the syringe is placed in contact with the cornea. The solid tip of the syringe does not touch the corneal surface, so that the danger of mechanical injury to the cornea is circumvented. The procedure is not painful if light topical anesthesia is used and if contact is made before the current is turned on and is maintained until after the current is off. The current should be increased and decreased gradually. Sudden making or breaking of the current is shocking to the patient. The voltage, amperage and duration of current applied vary with the circumstances; but, in any case, the ophthalmologist should proceed with caution. The only immediate injurious effect that we have observed from excessive application of iontophoresis has been a transitory stromal opacity; however, the long range effects of galvanic currents on the human cornea have yet to be determined.

I should like to stress that the concepts which I have presented are contemporary; i. e., they are based largely on recent and current research. They are not final, for much remains to be learned about the physiology of the cornea and its reactions to drugs and toxins; however, progress is being made more rapidly than at any time in ophthalmic history. It is noteworthy that in this contemporary research our colleagues in biochemistry and the other basic sciences are playing an important part. They are making applicable to ophthalmic problems technics and interpretations of physical and chemical phenomena beyond the scope of the usual medical education. Most of the notable contemporary work on the physiology and pharmacology of the cornea is resulting from teamwork between ophthalmologists and men with training and degrees in the basic sciences. With a number of such teams actively engaged in independent study, the contemporary concepts which I have presented are certain to be revised in the near future.

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INHERITANCE OF ARACHNODACTYLY, ECTOPIA LENTIS AND OTHER CONGENITAL ANOMALIES (MARFAN'S SYNDROME) IN THE E. FAMILY

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MARFAN'S disease is a syndrome which in its fullest expression is characterized by an elongate, slender body build, especially evident in the extremities; skeletal deformities (kyphosis, scoliosis, pigeon breasts, pes planus, hammer toes); dolichocephalic skull; poorly developed and hypotonic musculature; laxity of the joints and ligaments; scanty subcutaneous fat; malformation of the ears; malformations of the lungs; congenital heart disease and ocular anomalies, especially ectopia lentis. There is great variability in the degree to which these traits are expressed. The numerous publications which have appeared since the condition was first described by Marfan [1] in 1896, have been reviewed by Weve,[2] Burch,[3] Marfan,[4] Futcher and Southworth,[5] Clement [6] and Rados,[7] to whose papers the reader is referred for a complete bibliography and discussion of the syndrome. The articles by Lloyd [8] stimulated interest in the syndrome among American ophthalmologists.

From the Departments of Surgery and Medicine, the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

1. Marfan, A.-B.: Un cas de deformation congénitale des quatres mémbres, plus pronouncée aux extrémités, characterisée par l'allongement des os, avec un certain degré d'aminicissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220 (Feb. 28) 1896.

2. Weve, H.: Ueber Arachnodaktylie (Dystrophia mesodermalis congenita, Typus Marfan), Arch. f. Augenh. **104**:1 (May) 1931.

3. Burch, F. E.: Association of Ectopia Lentis with Arachnodactyly, Arch. Ophth. **15**:645 (April) 1936.

4. Marfan, A.-B.: La dolichosténomélie (dolichomélie, archnodactylie), Ann. méd. **44**:5 (June) 1938.

5. Futcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med. **61**:693 (May) 1938.

6. Clement, R.: La dolichosténomélie, Presse méd. **47**:527 (April) 1939.

7. Rados, R.: Marfan's Syndrome, Arch. Ophth. **27**:477 (March) 1942.

8. Lloyd, R. I.: Arachnodactyly (Dystrophia Mesodermalis Congenita, Typus Marfan, Marfan's Syndrome, Dolichostenomelia), Arch. Ophth. **13**:744 (May) 1935; A Second Group of Cases of Arachnodactyly, ibid. **17**:66 (Jan.) 1937.

The present communication will describe an extensive new pedigree of Marfan's disease, with emphasis on the ocular abnormalities, and will consider at some length the hereditary aspects of the disease.

THE E. FAMILY

The clinical records of several hundred visits by members of the E. family have been accumulating at the Strong Memorial and Rochester Municipal Hospitals since 1928, shortly after the two hospitals were opened. In 1941, an attempt was made to examine as many as possible of the kindred who had not yet been seen, and to reexamine all the members who had hospital records. In addition, all the available records were reviewed. Most of these persons were suspicious of examination

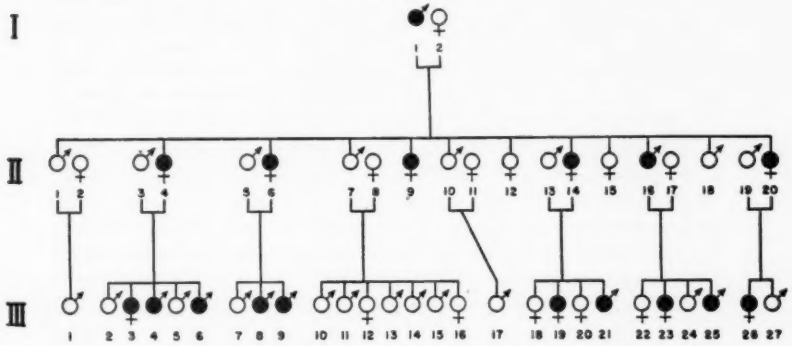

Fig. 1.—Pedigree of the E. kinship. Solid circles indicate members who certainly or probably had Marfan's disease; plain circles indicate normal members.

and were poorly informed about other members of the family. Repeated efforts to induce some of these persons to submit to an ophthalmologic examination have been fruitless.

The pedigree of this family is shown in figure 1. Of the 40 members, exclusive of spouses, who compose this pedigree, 27 have been examined by ourselves or by other members of the hospital staff, sometimes only once, usually repeatedly. Five of the remaining 13 persons are dead. It is felt that 17 persons in this pedigree may have had Marfan's disease, and such members are indicated in figure 1 by solid black symbols. Fourteen of these 17 persons who are thought to have had the disease have been examined at the hospital. The first person recognized as having the syndrome was *II 20*. In this pedigree there is the well known variation in the expression of the syndrome. Some of the members show the disease in so mild a form that were it not

for the presence of the typical syndrome in their siblings, or their transmission of the disease in its more typical form to their children, the diagnosis would be in doubt. The variability of the disease and the occurrence of a forme fruste will be discussed later.

The first generation of this family, *I 1* and *I 2*, came to this country from Germany some time before 1900. Both were Jewish, as were the persons who married into the family. There have been no known consanguinous marriages. Nothing is known of the ancestors in Germany. The mother, *I 2*, had in this country a brother with 4 children and a sister with 1 child; all are believed to have had good vision and physique. No relatives of the father, *I 1*, are known to be in this country. *I 1* and *2* were described as about 5 feet 5 inches (165 cm.) tall and rather obese. Further information on the physical characteristics is lacking, other than that the father, *I 1*, had a spinal curvature. A similar deformity occurred in one of his sons, *II 16*, who is believed to have Marfan's syndrome. The parents died at about the age of 52—the mother of diabetes and gangrene of the leg; the father suddenly, of a heart attack. The father, *I 1*, lost the sight of one eye during the last years of his life, there being a vague history of trauma, and later, without known cause, he suddenly became blind in the other. We interpret this condition to have been acute bilateral glaucoma, secondary to dislocated lenses, and consider him the progenitor of the syndrome in the family.

An attempt has been made to obtain information on the 8 spouses of members of the family who are illustrated in the pedigree, in order to determine to what extent they may have been the source of the various aspects of Marfan's syndrome seen in some of their children. Four of these spouses have not been seen but are thought to be normal. Four have been examined in the hospital. One of these, *II 5*, when hospitalized because of left inguinal hernia, at the age of 36, was noted to be asthenic, with a height of 185 cm. and a weight of 62.8 Kg. Another member, *II 17*, was found, at the age of 32, to have a soft apical systolic murmer and right exotropia of about 30 degrees. *II 13*, who had an occlusion of the coronary arteries at the age of 42, was 5 feet 5 inches in height and was of obese, pyknic type.

DESCRIPTION OF THE PEDIGREE

A detailed description of the pedigree follows. Only the more significant data on each person are presented.

II 1: A. E., a man aged 49, was described by his sisters as 5 feet 11 inches (180 cm.) in height, obese and wearing "thin" glasses.

II 4: A. B., a woman aged 45. We have been able neither to see nor to obtain a completely satisfactory description of this woman; she is thought to be of average body build. However, she has had visual difficulty for many years, and in 1934 it was noted on one of her children's records (whom she must have accompanied to the eye clinic) that she was wearing a correction of +18.75 D. sph. for the right eye and +8.25 D. sph. for the left eye, from which notation we conclude that she has dislocated lenses. Inasmuch as she had 3 children with Marfan's disease, she is thought to have the syndrome.

II 6: F. H., a woman, died at the age of 33. Body measurements are given in table 2. She was admitted to the hospital in 1934, at the age of 33, because of a cystocele and rectocele and a third degree retroversion of the uterus. In addition to complaints referable to the pelvis, she had experienced dyspnea and orthopnea during the preceding year and had had episodes of what was probably paroxysmal tachycardia several months before admission. She also complained of a chronic cough. The history was difficult to evaluate. She had been observed in the outpatient department for a month prior to her admission to the hospital, and no objective evidence of cardiac decompensation had been noted. There was no history of rheumatic fever or of chorea. The reproductive history was of some interest in that three of six pregnancies had terminated in early miscarriages.

She was described as well developed but nervous and as appearing chronically ill, with a skeletal system of moderate size and no abnormal curvatures. Aside from the pelvic abnormality, the chief findings of significance related to the heart. The heart appeared to be slightly enlarged on percussion. A loud apical systolic murmur was transmitted to the axilla, and a soft systolic murmur, heard in the aortic area, could be traced to the vessels of the neck. The pulmonic second sound was greater than the aortic second sound. The blood pressure was 125 systolic and 75 diastolic. The pulse rate was 88. The lungs were clear. A posteroanterior roentgenogram of the chest revealed slight enlargement of the heart in the region of the left ventricle and a prominence in the region of the left auricle. The electrocardiogram was normal. The impression was that of rheumatic heart disease with mitral insufficiency, together with questionable aortic involvement, which was well compensated. There was no record of ophthalmologic examination, but she was known to have had the family ocular trouble and to have worn thick glasses.

After amputation of the cervix, radical cure of the cystocele and rectocele, uterine suspension and a salpingo-oophorectomy on the left side, she exhibited obstructive urinary retention. This was relieved the second day, when the nonprotein nitrogen was 76 mg. per hundred cubic centimeters. Fluids were forced conservatively. Acute cardiac decompensation then developed, and, despite vigorous supportive measures, she died on the fourth postoperative day. In retrospect, it would seem that the heart murmurs may have been congenital; these, together with the ocular anomalies, would lead to the diagnosis of Marfan's syndrome, even though the patient appears to have been of average build. The postoperative course suggests a low cardiac reserve. Two of her children showed stigmas of Marfan's disease, one of them, *III 9,* in rather extreme form (fig. 3 *A* and *B*).

II 7: L. E., a man aged 44, had been admitted to the hospital at the age of 42 for repair of right inguinal hernia; the physical status was otherwise normal. His height was 164.5 cm. and his weight 62 Kg.

II 9: L. E., a girl, died at the age of 19. She was reported to have been very slender, with a "crippled" arm and leg. The condition of the eyes was unknown. She was said to have died suddenly, at the age of 19, of a "heart attack." On this evidence she is believed to have had Marfan's syndrome.

II 10: J. E., a man aged 39, was reported as normal.

II 12: B. E., a girl, died in infancy, of unknown cause. She was thought to have been normal.

II 14: S. C., a woman aged 37 (figs. *2 A* and *5 a;* refraction, vision and measurements in tables 1 and 2), was first seen at the age of 36, during the follow-up studies on her kindred; her only complaint was painful feet. General medical examination revealed that she was moderately obese with, however, rather slender extremities. In spite of an excessive amount of subcutaneous fat over the body,

her light skeletal framework and musculature were evident. She had rather narrow, stooped shoulders with moderate kyphosis of the dorsal portion of the spine and wide hips. She stated that she had gained 79 pounds (35.8 Kg.) in the past ten years; her picture indicated that she must previously have been slender. There were no abnormal cardiac findings. She had a first degree cystocele and rectocele. Orthopedic examination revealed narrow feet with second degree pronation and bilateral hallux valgus, with heavy callosities over the tarsal and metatarsal joints. She walked toeing straight forward.

TABLE 1.—*Refraction and Vision in Ten Members of the E. Kinship with Marfan's Syndrome*

Member	Age, Yr.	Right Eye: Refraction and Vision	Left Eye: Refraction and Vision
II 14	37	— 2.00 ⊂ —2.00, ax. 130 = 6/20	— 2.00 ⊂ — 4.50, ax. 60 = 6/20
II 20	24	+ 0.50 ⊂ —5.50, ax. 180 = 6/15	+ 0.50 ⊂ — 5.50, ax. 180 = "Amblyopia"
III 3	22	+10.50 ⊂ +1.50, ax. 95 = 6/15	+11.00 ⊂ + 1.25, ax. 60 = 6/60
III 4	20	+10.75 ⊂ +0.50, ax. 95 = 6/10—1	+10.75 ⊂ + 0.50, ax. 50 = 6/60
III 6	17	+12.00 ⊂ +0.25, ax. 90 = 6/15—1	+12.00 ⊂ + 1.50, ax. 160 = 7/200
III 8	12	—6.00 = 6/20+2	—4.00 = 6/30
		+ 7.50 ⊂ +3.50, ax. 115 = 6/30	+ 8.00 ⊂ + 3.00, ax. 100 = 6/30
III 9	15	+ 8.00 ⊂ +2.00, ax. 90 = 6/7.5—3	+ 4.75 ⊂ + 1.25, ax. 90 = 4/200
III 19	18	— 0.50 ⊂ —5.00, ax. 165 = 6/12	— 3.00 ⊂ — 5.00, ax. 170 = 6/20
III 21	8	+10.50 ⊂ +1.50, ax. 110 = 6/15	+ 9.00 ⊂ + 0.75, ax. 70 = 6/15—2
III 26	9	— 5.00 ⊂ —2.50, ax. 30 *	— 4.50 ⊂ —11.50, ax. 170
		+10.00 ⊂ +3.00, ax. 120	+12.50 ⊂ + 0.50, ax. 80

* Retinoscopy.

TABLE 2.—*Measurements for Twelve Members with Arachnodactyly in the E. Kinship*

Members	Sex	Age, Yr.	Height (Cm.)	Weight (Kg.)	Normal Weight for Height*	Span (Cm.)	Skull Measurements (Cm.)		Cephalic Index
							Antero-posterior	Trans-verse	
II 6	F	33	168.0	63.4	66.1	.....	....	....	....
II 14	F	36	167.5	83.4	66.6	167.5	17.7	14.0	78.8
II 16	M	37	160.0	50.0	60.4	.....	....	....	....
II 20	F	27	163.0	33.2	61.5	164.0	19.0	14.0	73.7
III 3	F	22	168.0	56.8	61.8	172.5	19.5	15.0	76.9
III 4	M	20	184.5	76.4	77.7	187.5	20.5	15.5	75.6
III 6	M	17	172.5	70.4	69.7	178.5	19.5	14.5	74.4
III 9	M	15	184.5	54.0	73.6	192.0	17.6	15.0	85.2
III 19	F	18	166.8	51.6	57.4	170.8	18.5	14.5	78.4
III 21	M	8	135.0	28.4	29.4	135.0	18.6	13.5	72.6
III 23	F	5	128.5	22.0	....†				
III 25	M	6	119.0	20.4	22.3				

*From Martin, R., and Bach, F.: Grössen- und Massen-Verhältnisse beim Menschen, Tabulae Biologicae, 1926, vol. 3, p. 617. Deaver, G. G.: Fundamentals of Physical Examination, Philadelphia, W. B. Saunders Company, 1939.

† This child is so tall for her age that no standard figures are available for comparison.

She had worn glasses for the past twenty years. Ophthalmologic examination revealed that the interpupillary distance was 54 mm. The eyeballs were of average size. The scleras were normal. The corneas measured 10.5 by 11.5 mm. The pupils were 3 mm. in diameter and oval, with the long axis in the right eye at

45 degrees and that in the left eye at 130 degrees. The pupils were reactive, and the iris frill was normal except for a pupillary membrane, in the form of an inverted Y, in the right eye. With paredrine hydromide ophthalmic® (a 1 per cent solution of *p*-hydroxy-α-methylphenylethylamine hydrobromide in distilled water, made isotonic with 2 per cent boric acid and preserved in merthiolate, 1:50,000) and homatropine, the pupils dilated to 5 mm. in diameter and were round. The irises were olive colored with a faint yellow wash in the pupillary zone and no

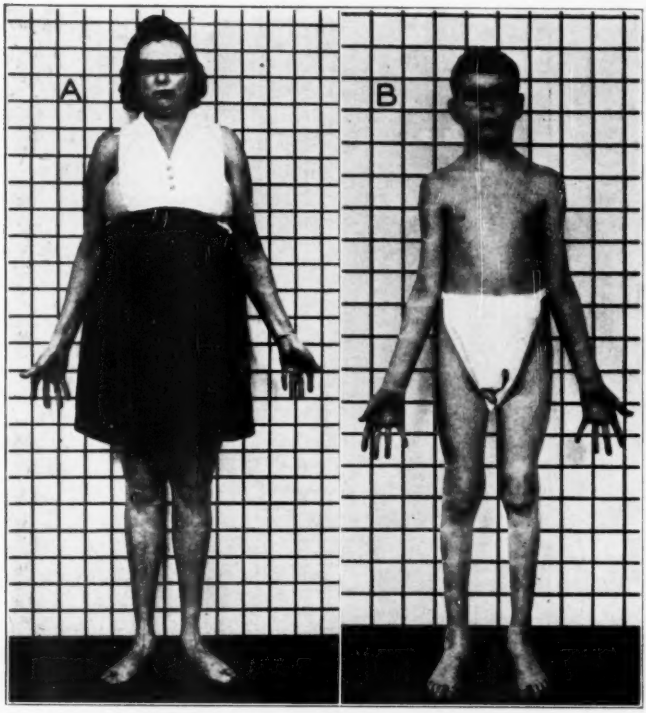

Fig. 2.—*A*, front view of *II 14*, aged *37*; *B*, front view of *III 21*, aged 9, son of *II 14*. Both these members had ectopia lentis, but the skeletal changes were minimal, and there were no abnormal cardiac signs.

additional markings. They trembled in the lower nasal quadrants. On scleral transillumination, light passed through the outer two thirds of both irises in radial spokes. The lenses, of average size, were dislocated upward, temporally and slightly backward. They did not tremble with ocular movements. A few small white opacities were scattered through the lenses, which were slightly yellow. No posterior zonular fibers were present. The anterior fibers were evenly spaced. None were broken. The vitreous bulged slightly forward behind these tightly

stretched suspensory fibers. The deeper filaments of the vitreous were more opaque than usual. The optic disks were of the closed type, with a prepapillary membrane on the lower third of the left disk. The retinas were normal. The choroidal vessels were visible. The tension was 21 mm. (Schiøtz) in each eye. Ishihara charts for color vision were all read correctly.

The patient's condition would appear to represent a forme fruste of the disease.

II 15: R. E., a girl, died at the age of 2 years, of whooping cough.

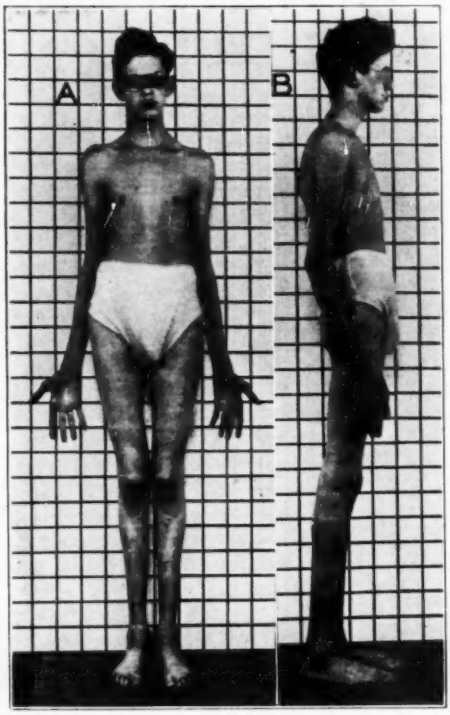

Fig. 3.—Front and profile views of *III 9*, aged 16. He presented arachnodactyly, ectopia lentis and an apical systolic murmur.

II 16: M. E., a man, was first hospitalized in 1944, at the age of 34, for cardiac decompensation with dyspnea. He was hypermetropic and had worn heavy glasses since he was 5 years of age. The social service record showed inability to hold steady employment because of his defective vision, particularly for close work. His sisters described him as slender and stated that his vision and general health had always been poor. He had prominent dorsal kyphosis and reduction in the antero-posterior diameter of the chest. A loud systolic murmur was heard over the

entire precordium. A roentgenogram showed curvature of the upper portion of the spine to the left, with compensatory curvature of the lower thoracic portion to the right. The left thoracic cage was considerably narrowed as a result of the scoliosis. The heart was enlarged in the transverse diameter. Fluoroscopic examination showed that the heart was increased in size with some mitral configuration, which was accentuated by the scoliosis to the right. There was increased prominence of the conus. A calcified valve, believed to be the mitral, was seen.

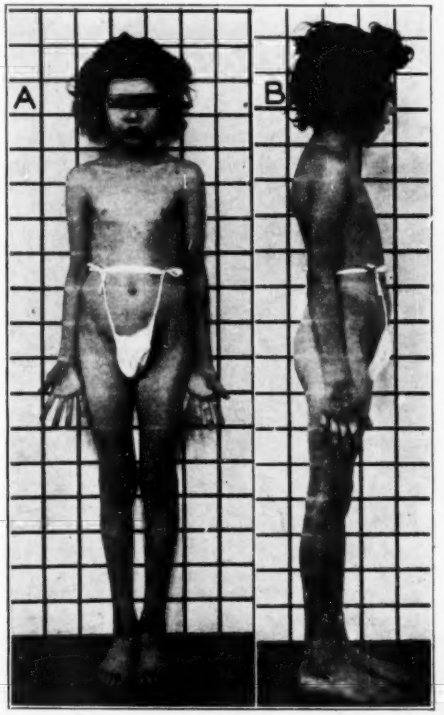

Fig. 4.—Front and profile views of *III 23*, aged 6. This child was under observation for three years in a cardiac clinic, with a diagnosis of congenital heart disease. After her relationship to the E. family was discovered, ophthalmologic examination revealed minimal inferior colobomas of the lenses. The body configuration would not ordinarily excite comment.

The patient stated that the curvature of his back had been present since infancy and was like his father's. A diagnosis was made of rheumatic heart disease with lesions of the mitral and aortic valves. He denied having a history of rheumatic fever. He was again hospitalized and died of cardiac decompensation in 1947, at the age of 37. Except for the kyphosis and scoliosis, the only significant abnormalities observed at autopsy related to the heart (Dr. W. B. Hawkins).

Heart: The heart weighed 670 Gm. The epicardium was smooth, with a small quantity of yellow fat and multiple petechial hemorrhages over all its surfaces. The chambers were dilated and contained friable, postmortem clots. There were no congenital abnormalities. The endocardium was smooth and glistening. The tricuspid valve measured 13 cm.; the pulmonary, 7.5 cm.; the mitral, 15 cm., and

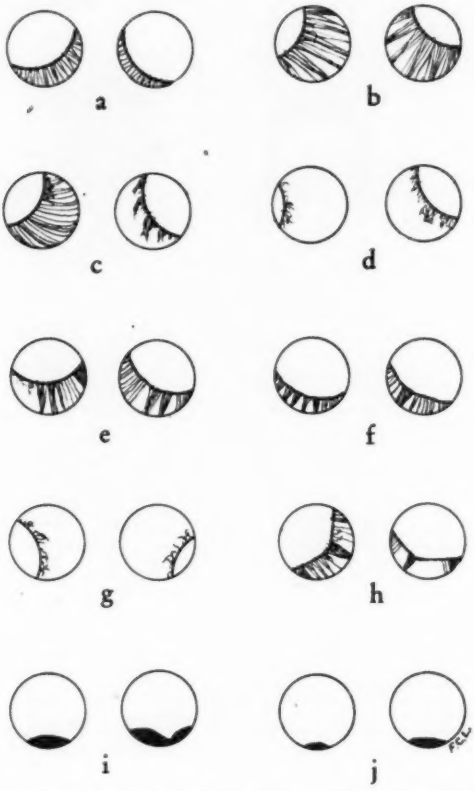

Fig. 5.—Lenses and zonular fibers in 10 members of the E. kinship with Marfan's syndrome, as seen by slit lamp (*a–h*) or ophthalmoscope (*i* and *j*). With the latter instrument, the inferior colobomas of the lenses appear as black notches. Here *a* is *II 14*; *b*, *III 3*; *c*, *III 4*; *d*, *III 6*; *e*, *III 9*; *f*, *III 19*; *g*, *III 21*; *h*, *III 26*; *i*, *II 20*, and *j*, *III 23*.

the aortic, 11 cm. The leaflets of the tricuspid and pulmonary valves were thin and delicate. The leaflets of the mitral and aortic valves were slightly thickened, and the edges were rolled. There were two calcified plaques just inferior to the mitral ring. Both the aortic and the mitral valve appeared to be incompetent. The root of the aorta was dilated and contained many small atheromatous plaques,

particularly around the ostiums of the coronary vessels. The thickness of the wall of the left ventricle was 2.4 cm., and that of the wall of the right ventricle 0.6 cm. The myocardium was firm and reddish brown. There were no visible gross lesions. The coronary vessels were patent but contained many atheromatous plaques.

Microscopic sections through the aortic valve and the left ventricle showed an increase in collagenous tissue in the vicinity of the ring, replacement of some muscle fibers with collagen, thickening of the leaflet, increase in fibrous tissue between muscle fibers and bundles and hypertrophy of some muscle fibers. Other sections through the left ventricle showed the same myocardial degeneration. There were also areas of endocardial thickening. A thrombus was present in the auricular appendage of the right auricle, and the wall showed degeneration and lymphocytic infiltration.

The anatomic diagnosis was chronic rheumatic endocarditis of the aortic and mitral valves, aortic and mitral insufficiency, myocardial fibrosis, cardiac hypertrophy and dilatation, thrombosis of the right auricular appendages, mild generalized arteriosclerosis, congestion of the viscera with central necrosis of the liver, edema of the lower extremities, edentia, kyphosis and scoliosis.

The probability that this patient had Marfan's disease was not recognized until after his death, when his record was reviewed in relation to the study of this family. From the history, his case is regarded as one of Marfan's disease.

II 18: S. E., a man aged 32, had a normal appearance and vision.

II 20: D. G., a woman, who died at the age of 27 (fig. 5*i*; refraction, vision and measurements in tables 1 and 2), was the proband in this study. She was examined in 1943 in a sanatorium five months before her death from tuberculosis. At this time she was weak, emaciated, and extremely asthenic, due no doubt in part to the ravages of tuberculosis; yet she stated that she had never weighed over 98 pounds (44.5 Kg.). There were pronounced lumbar lordosis and dorsal kyphosis. The bones were small and delicate, and the musculature poor. The palate was high. The ears had a large, prominent lobule and tragus. The thoracic cage was long, with the lower boundary only 2.5 cm. above the crest of the ilium. The extremities were thin, with hypermotility of all the joints, so that she could touch the thumb to the wrist with ease and could touch the little finger to the thumb over the back of the proximal phalanges. The fingers and toes were long and tapering, with slight clubbing of the thumb and great toes. In walking, she toed straight forward. There were no cardiac abnormalities.

Vision had been poor "since birth." The eyeballs were of average size. The irises were olive colored, smooth and without crypts or markings. They could be transilluminated in the peripheral third and were tremulous in the lower portion. Ophthalmoscopically, through pupils dilated to 7.5 mm. in diameter, the lower border of the right lens was visible as a single notch and the lower border of the left lens as a double notch. The media appeared clear. The fundi were not unusual; the disks were of the normal, closed type. On the upper third of the left disk was a prepapillary membrane. The Ishihara charts for color vision were correctly read.

She is thought to represent a patient with rather typical Marfan's disease.

III 1: A. E., a man aged 20, was reported to have left internal strabismus, but was otherwise normal.

III 2: H. B., a youth who died at the age of 16 by drowning, was seen in the hospital in 1933, at the age of 14, because of nonspecific facial lesions; nothing unusual otherwise was noted except for slight facial asymmetry. His height at the age of 14 was 168.5 cm. and his weight 64.2 Kg.

III 3: R. B., a woman aged 22 (fig. 5*b*; refraction, vision and measurements in tables 1 and 2), has been seen repeatedly in the clinics. Development was somewhat retarded: The first teeth were cut at 9 months; she walked at 16 months and talked at 2 years of age. She was repeatedly described as slender, with long extremities and generally poor physical development. Her face was long and had an aged appearance. The teeth showed crowding and malposition. There was dorsal kyphosis. Pes planus was prominent on the left. There was a high degree of talipes equinovalgus of the right foot; in walking, her weight was borne on the inner border of the everted right foot. The height at the age of 12½ years was 163 cm. and the weight 43 Kg. There were no significant cardiac findings in childhood; at the age of 22 a soft apical systolic murmur was noted.

Vision had been poor since early childhood. A sketch of the lenses at the age of 7 showed them to have been in the same position as at the age of 22 (fig. 5*b*). On her last examination, at the age of 22, the interpupillary distance was 54 mm. The eyeballs appeared a little larger than average. The corneas measured 11 by 12 mm. The scleras were slightly grayish. The anterior chambers were of greater than average depth, and the lower two thirds of the irises were tremulous. The latter were olive colored, with a faint yellow washing, and were without surface crypts. The entire peripheral third of both irises could be transilluminated as radiating fine spokes, and the ciliary region was more transilluminable than usual. The iris frill was reduced in height. Tension was 16 mm. (Schiøtz) in each eye before and after dilation with homatropine hydrobromide. Number 6 metric print could be read with a +3 sphere added to the correction for the right eye, but no small print could be read with the left eye. The lenses were clear, slightly spherical and dislocated upward and outward, as well as backward, away from the irises. The zonular fibers passed across the aphakic area in groups. Only a few fibers were broken; these hung loosely from the border of the lens. Most of the fibers which were broken were posterior fibers. The bulging vitreous possessed a normal-appearing anterior layer. The filaments of the deep portion of the vitreous were more opaque than average. The fundi were normal, with no choroidal circulation visible and with deep physiologic cupping of the optic disks. All the Ishihara charts for color vision were read correctly.

The patient is regarded as having a typical Marfan's syndrome.

III 4: J. B., a man aged 21 (fig. 5*c*; refraction, vision and measurements in tables 1 and 2), was first seen at the age of 10 because of impetigo and underweight (height 147.8 cm.; weight, 31.4 Kg.). He was poorly developed and poorly nourished, with a long thoracic cage; the chest had a definite Harrison groove. Both lenses were dislocated. There was nothing unusual about the heart. When reexamined at the age of 20, he was noted to be well developed, but to have slender extremities and long hands and feet. There was pes planus. A soft apical systolic murmur was present. Physical examination otherwise revealed nothing remarkable.

Vision had been poor since childhood. There were 20 degrees of left exotropia for near and 30 degrees for far vision. The eyeballs were a little larger than average and the anterior chambers of greater than average depth. The pupils were 4 mm. in diameter and oval. On the right the long axis was at 110 degrees and on the left, at 70 degrees. The irises were pale blue. The yellow-tinged pupillary region was also oval in the same axis as the pupils. The pigment collar of the pupil was practically absent. Iridodonesis was present bilaterally. The outer two fifths of the iris could be transilluminated as radial spokes, this appearance being increasingly pronounced toward the base of the iris. Scattered areas in the ciliary region could be transilluminated. The scleras were diffusely transilluminable, like an eggshell. The lenses were dislocated upward and temporally,

and a few punctate opacities were scattered throughout. On the right lens the lower zonular fibers were intact and evenly spaced. The upper posterior fibers were broken and floated free from the margin of the lens. The anterior fibers in this region were intact. The left lens trembled with the ocular movements. All visible zonular fibers were broken and hung from the border of the lens. The anterior vitreous was not visible in either eye. Deep in the posterior segment of the vitreous were a few filaments scattered with pigment granules. The fundi were normal. Tension was 16 mm. (Schiøtz) in each eye before and after dilation. Tests with the Ishihara charts showed total color blindness.

On the basis chiefly of the pathologic condition of the eyes, his case is regarded as one of Marfan's syndrome.

III 5: R. B., a youth aged 19, was referred to the hospital at the age of 9 years because of "malnutrition"; but the height and weight were normal (height, 129.8 cm.; weight 27 Kg.), and physical examination revealed nothing abnormal. He was seen at the age of 15 because of diarrhea. The physical status was again found to be normal except for a soft apical systolic murmur. At the age of 19, he was reported by his sisters to be of normal, stocky build (height, 5 feet 6 inches [167.6 cm.]; weight, 155 to 160 pounds [72.6 Kg.]).

III 6: K. B., a youth aged 18 (fig. 5*d*; refraction, vision and measurements in tables 1 and 2), has been seen repeatedly at the hospital, with his first visit at the age of 7 because of apparent malnutrition, scabies with secondary infection and poor near vision, the last disorder being due to dislocated lenses. The height was 122.7 cm. and the weight 22.4 Kg. Hypertrophied tonsils were also observed at the first visit. The patient was always a thin, gangling boy, with disproportionately long extremities. As a boy, his sternum was prominent, and Harrison's groove was present. There was pronation of the feet, more pronounced on the left. The heart was essentially normal. He was carefully studied at the age of 15 because of severe and increasing frontal headaches, of six weeks' duration. He was then a large boy of average build. The heart was normal. The knee jerks were sluggish. A roentgenogram revealed that the pineal gland was calcified and was located slightly higher than, and anterior to, the normal position. The sella turcica was within normal limits. Lumbar puncture yielded a fluid with normal dynamic status and chemical composition. No intracranial lesion could be demonstrated.

The eyesight had been poor "since birth." Examination of the eyes at the age of 18 revealed a fine horizontal nystagmus of 2 or 3 degrees, with the rapid component to the right, which was present with and without glasses. The eyeballs were of average size; the anterior chambers were deeper than usual. The irises were pale olive, with a faintly yellow coloration of the inner third and several specks of yellow in the middle third. They could be transilluminated, the outer third to a greater degree, as radial reddish spokes. The remainder of the eyeball was not unusually transilluminable. Through dilated pupils, the nasal edge of the right lens was barely visible and moved backward and forward as though on a temporal hinge. The right lens appeared abnormally small. All visible zonular fibers were broken and twisted on the edge of the lens. The lens was clear except for a few punctate opacities. There was no anterior vitreous in the right eye, and the posterior segment was continuous with the aqueous. Several thin filaments of vitreous were visible at the greatest depth of the slit lamp beam. The lens in the left eye was dislocated upward and temporally, with similar broken and twisted zonular fibers; but the lens did not tremble with movements of the eye. There were a few fine punctate opacities in the lens. There was no anterior vitreous in the left eye; only a single strand of posterior vitreous was visible at the greatest

depth discernible with the slit lamp. The maculas were poorly differentiated. The fundi were otherwise normal, with the peripheral choroidal vessels visible. Jaeger type 3 could be read with the right eye with a +3 sphere added to the correction, but even large print could not be read with the left eye. Tension was 15 mm. in each eye before and after dilation. Total color blindness was found with the Ishihara charts.

III 7: This member, a boy, died at the age of 3 months, of unknown cause. The small amount of information available does not permit of classification; he is shown on the chart as normal, in the absence of evidence to the contrary.

III 8: R. H., a youth aged 19 (refraction and vision in table 1), was first seen at the hospital at the age of 11 because of poor vision. Iridodenesis was present. The lenses were dislocated upward and temporally. At the age of 14 he was found to have two optical systems, either of which could be used. In 1940 vision could not be improved above 6/20 in each eye. Despite this, he was inducted into the Army, for which reason he could not be reached for study. The family reported that at the age of 18 he was 6 feet 4 inches (193 cm.) in height and weighed 165 pounds (74.8 Kg.). He is considered to have Marfan's disease.

III 9: H. H., a youth aged 16 (figs. 3 *A* and *B* and 5 *e*; refraction, vision and measurements in tables 1 and 2), has been seen repeatedly at the hospital, where his slender physique and small bones have frequently been commented on. He was first seen at the age of 6 because of episodes of pallor, emesis and collapse. His height was 125.5 cm. and his weight 20.2 Kg. Significant findings included bilateral dislocation of the lens; hypertrophied tonsils; tachycardia; borderline cardiac hypertrophy with a questionable apical middiastolic murmur; indirect inguinal hernia on the left side; inversion of the feet, with pes planus on the left; underweight, and dental caries. The question of rheumatic heart disease was raised. The possibility of petit mal was entertained. However, these episodes soon ceased, and the diagnosis was not verified. At the age of 7 he was in a sanatorium for tuberculous patients, although an active lesion does not seem to have been demonstrated. The following year the left indirect inguinal hernia was repaired. Physical examination made at the age of 15, in connection with the study of this family, showed a slender youth with disproportionately long extremities (fig. 3 *A* and *B*). The ears were large and floppy, with few convolutions. The thoracic cage was long and narrow, with a reduced anteroposterior diameter. At rest the circumference of the chest was 30.5 inches (77.5 cm.); at full expansion it was 31.5 inches (80 cm.), and at complete expiration 29.5 inches (74.9 cm.). The normal lumbar lordosis was replaced by kyphosis in the upper part of the region. There was a slight left scoliosis; the scapulas were winged, and the long borders of the scapulas were conspicuously concave. The sternum was depressed, with a strong ridge at the sternocostal junction. The hands and feet were unusually large, especially in proportion to the slender wrists and ankles. There was hypermobility of the joints. Pes planus was pronounced. The patient toed in when walking. There were numerous scattered areas of dilated blood vessels in the skin of the back. The palate was high and the teeth were carious. The heart appeared somewhat enlarged, with the apex 2 cm. beyond the midclavicular line. A soft apical systolic murmur was heard. The blood pressure was 114 systolic and 60 diastolic. The genitalia were large and normal. The tendon reflexes were sluggish.

The interpupillary distance was 52 mm. The eyeballs appeared larger than average. The corneas measured 10.5 by 11.5 mm. The anterior chambers were of average depth. The left pupil was displaced 1 mm. nasally. The irises were pale blue with a few yellow markings, and the lower halves were tremulous. On transillumination, the peripheral third of the irises appeared practically without

pigment. The pupils dilated to 7 mm. with paredrine® and homatropine. The lenses appeared a little smaller than usual. A large clump of granules of sharp-angled, light brown pigment was visible on the lower posterior surface of the right lens, which was dislocated upward and temporally. Temporally, the zonular fibers of this lens were ruptured. Two groups of both anterior and posterior fibers were attached to the inferior border of the right lens. Next to these, in the lower nasal aphakic region, the fibers were intact and evenly spaced, but the posterior fibers appeared finer than usual. A bundle of large anterior and posterior fibers crossed the nasal aphakic region. All fibers were tightly stretched; the anterior vitreous bulged forward behind them. In the left eye, two heavier groups of both anterior and posterior fibers ran almost vertically, while nasally and temporally the suspensory fibers were more evenly spaced. These suspensory fibers were more numerous anteriorly than posteriorly. Fine notches were present in the curvature of the lens border. The vitreous of the right eye appeared clear on ophthalmoscopic examination. In the left eye the vitreous showed many stringy opacities. It was difficult to differentiate the macula from the surrounding retina in either eye. The choroidal circulation was visible. There was slight physiologic cupping of the disks. The smallest print the patient could read with the right eye was no. 5 metric with a +3 sphere added to his correction. He could read no small print with the left eye. The Ishihara charts showed total color blindness.

Roentgenograms of the skull were not remarkable except for thinning of the cortex. The pulmonary fields were clear, and the cardiac silhouette was normal in roentgenograms. Films of the forearms, hands and feet showed an elongated bony structure with a tendency to narrowing of the diameter of the shaft. The epiphyses were normal for one of the patient's age. It was felt that, in addition to findings consistent with arachnodactyly, there was evidence of an old rachitic process.

III 10: I. E., a youth aged 19, was hospitalized at the age of 16 because of pneumonia. Except for signs at the base of the left lung the only unusual finding was a soft apical systolic murmur.

III 11, 12 and *13:* P. E., a boy aged 16; E. E., a girl aged 15, and H. E., a boy aged 14, were seen at their home, where they were subjected to a superficial appraisal and ophthalmoscopic examination. The only unusual finding was a prepapillary membrane on the nasal middle third of the left nerve head in P. E. (*III 11*).

III 14: A. E., a girl aged 7, was reported as normal by the other children.

III 15: L. E., a boy aged 5, was seen at the age of 4 because of acute nasopharyngitis, at which time he was otherwise normal.

III 16: B. E., a girl aged 2, born at Rochester Municipal Hospital, was a typical mongolian idiot.

III 17: E. E., a youth aged 17, was reported as normal.

III 18: M. C. H., a woman aged 21, had been seen at intervals because of allergic rhinitis and most recently, pregnancy. Her height was 130 cm. and her weight 61.4 Kg. She was of robust, pyknic habitus, with no skeletal abnormality. She had no visual complaints, and ophthalmologic examination revealed a normal status.

III 19: H. C., a girl aged 19 (fig. 5*f*; refraction, vision and measurements in tables 1 and 2), has been seen many times at the hospital, and her slender body build and elongate extremities have been commented on repeatedly. At the age

of 2½ years, her height was 99.3 cm. and her weight 13 Kg. At the age of 12½ years (height 155.5 cm. and weight, 32.6 Kg.), before the presence of Marfan's syndrome in the kindred had been recognized, the tentative diagnosis was hyperpituitarism with excessive growth of the long bones, mental retardation and dislocated lenses. She also had hypertrophied tonsils. When last seen, at the age of 18, she was very slender, with pronounced dorsal kyphosis. The narrowness across the shoulders was striking. The hands and fingers were long and tapering, and the thumbs could be touched to the wrist with ease. The feet were flat, narrow and tapering, with long toes. The length of the foot was 25.2 cm. She walked toeing out. The osseous framework was light. Cardiac abnormalities were not observed on this or on any other examination.

Vision had been poor since early childhood. The irises were brown, smooth and without markings. The iris frill was almost absent. The lower portions of both irises trembled slightly. They were transilluminated in their outer third. The pupils dilated evenly to a diameter of 8 mm. The right lens was dislocated upward and nasally and was strikingly spherical. It was clear except for a few punctate opacities. On the border of the lens were fine notches. The zonular fibers were distributed in groups and were intact. Only a few posterior fibers were present. Round brown pigment granules were scattered over the fibers. The left lens was dislocated upward and temporally. The fibers were almost evenly spaced and about equal in number anteriorly and posteriorly. A group of large fibers drew the border of the lens out into an angle at their point of attachment, at 7 o'clock, and the visible border of the lens elsewhere was irregular. The anterior portion of the vitreous of both eyes bulged forward behind the zonular fibers and possessed a normal appearance. The fundi were normal, with slightly open disks. All the Ishihara charts for color vision were read correctly.

The patient is regarded as showing a typical Marfan's syndrome.

III 20: C., a girl, died at the age of 17 months, of bronchopneumonia. There were no known abnormalities.

III 21: A. C., a boy aged 9 (figs. 2 *B* and 5 *g*; refraction, vision and measurements in tables 1 and 2), was first seen at the age of 3 with acute bilateral mastoiditis; there were no other abnormalities. Dislocated lenses were discovered at the age of 6, when he came in because of poor vision. When he was examined at the age of 8 he appeared to be a well developed boy of average build, except that the distal portions of his extremities were rather thin and the hands and feet were large. He spoke with a lisp. Physical examination showed an essentially normal condition except for the eyes. Vision had "always" been poor. The interpupillary distance was 55 mm. The corneas measured 10 by 11 mm. The anterior chambers were of average depth. The irises were an olive color with a few spots of orange and were tremulous. About 1 mm. of the periphery of the iris could be transilluminated. The pupillary ruffs were normal. The pupils were oval. The long axis on the right was at 70 degrees, and that on the left, at 110 degrees. The pupils were dilated with atropine to a diameter of 7 mm., at which diameter the long axis of the right pupil was found to be at 110 degrees and that of the left pupil at 80 degrees. The lenses were clear, of average size and displaced downward, outward and backward from the irises. All the visible zonular fibers of both lenses were broken and were twisted together at the border of the lens. The lenses trembled with the movements of the eyes. There was no demarcation between the aqueous and the anterior portion of the vitreous, and only a few vitreous filaments floated in a clear, aqueous-like fluid which filled the posterior segment of the

eye. Ophthalmoscopically, there were a few opacities in the vitreous, being more numerous on the left. The choroidal circulation was visible over the whole of both retinas, including the central areas. The maculas were difficult to differentiate. The disks were of the normal closed type.

A posteroanterior roentgenogram of the chest revealed nothing remarkable. Roentgenograms of the forearms, legs, hands and feet were interpreted as showing that the length of the long bones was somewhat increased and that the phalanges were definitely longer than usual. The bony development was consistent with the chronologic age.

In this case only the ocular abnormalities are definitely present; nevertheless, the diagnosis of Marfan's syndrome seems justified.

III 22: E. E., a girl aged 10, when examined, at the age of 4, preliminary to a tonsillectomy, was described as an asthenic, underweight child; but there were no cardiac abnormalities or any evidence of ocular disease. On the basis of this evidence, as well as that of statements of other members of the family, she is believed to be a normal child.

III 23: T. E., a girl aged 6 (figs. 4 *A* and *B* and 5 *j*; measurements in table 2), at the age of 2½ years (height, 113 cm.; weight, 17.8 Kg.) was referred to the clinic because of a heart murmur; and a diagnosis of organic heart disease was made on the basis of an apical thrust and a shrill apical systolic murmur which was transmitted to the axilla. Roentgenographic and fluoroscopic examinations of the chest revealed no cardiac enlargement. She was kept under observation because of the heart murmur, which was first considered of rheumatic origin and was later thought to be caused by congenital heart disease. At the age of 5 her relation to this pedigree of Marfan's syndrome was first established. Her last examination, at the age of 6, showed a very tall, rather slender girl with long hands and feet (fig. 4 *A* and *B*). She tended to toe in as she walked. Aside from the habitus illustrated by the photographs (and this was certainly not striking), the significant findings pertained to the heart and eyes. There were prominent pulsations in the fourth and fifth intercostal spaces. The maximal precordial impulse was felt in the fifth interspace in the anterior axillary line. Percussion confirmed this finding. A palpable systolic thrill was felt over the apex. The heart sounds were regular and loud, with a rate of 140 to 150 a minute. A soft, blowing apical presystolic murmur was followed by a rough systolic murmur. The blood pressure was 110 systolic and 54 diastolic. Rotengenographic and fluoroscopic studies of the chest revealed unusual prominence in the region of the left auricle and apparent enlargement in the region of the left ventricle. Ophthalmoscopic examination, with the eyes rotated downward and the pupils fully dilated, revealed small black notches in the lower edges of both lenses. The fundi were best visualized with a —4 D. lens. No abnormalities of the fundi were noted.

III 24: G. E., a boy aged 8, when hospitalized for tonsillectomy had no recorded cardiac abnormalities, but a pronounced cardiac enlargement of mitral type was found on roentgenograms. Insufficient information is available to permit the diagnosis of Marfan's disease to be made in this case.

III 25: M. E., a boy, in 1947, at the age of 6, had left esotropia of 15 degrees. One half of each dilated pupil was aphakic. The right lens was displaced upward and temporally; the left lens temporally and very slightly upward. Retinoscopic examination gave a correction of +6.00 D. for the right eye and +7.00 for the left eye. Vision was not obtainable. The chest was reported as showing a funnel

deformity of moderate degree. The fingers and toes were unusually long. Although the heart sounds were recorded as normal, pronounced cardiac enlargement to the left was found roentgenologically. He appeared slow, but not retarded mentally. This member has the characteristics typical of Marfan's disease.

III 26: M.G., a girl aged 10 (fig. 5*h*; refraction and vision in table 1), was first seen at the age of 7 months because of bilateral otitis media. When examined at the age of 9, she was an attractive, intelligent, extremely thin child with a long face and delicate, slender extremities. The length of the fingers was striking. General physical examination revealed nothing abnormal.

Vision had been poor since early childhood. The eyeballs appeared a little larger than usual. The corneas measured 11.5 by 12 mm. The anterior chambers were of average depth. Both irises were tremulous and could be transilluminated, particularly at the periphery. Both lenses were dislocated upward and temporally. The right lens was more spherical than usual. It was slightly hazy throughout, with faint posterior cortical opacities. A few anterior zonular fibers drew the border of the lens out into an angle at 3:30 o'clock. On both sides of the group the fibers were ruptured. Except for this group of fibers and two others located, respectively, at the upper and lower edges of the lens, as seen through a fully dilated pupil, no anterior fibers were present, and there were no white dots along the periphery of the lens to which the anterior fibers were attached. A few brown pigment granules were scattered over the fibers. The anterior vitreous behind the posterior suspensory fibers appeared normal.

The left lens appeared thinner than average and slightly opaque, with small, scattered white opacities. The lens was drawn into an angle at 7:30 o'clock by a group of individually large anterior and posterior suspensory fibers. On either side of this region there was complete absence of the fibers, with no visible points of previous attachment along the lens border. Above, in the aphakic region, evenly separated, very fine posterior fibers could be seen, but no anterior fibers. Individually, these fibers were about one-third the caliber of the large ones attached at 7:30 o'clock. At 4 o'clock there was a group of evenly spaced anterior and posterior fibers of average size. A faint anterior peripheral cortical opacity was in the same axis with the large group of fibers at 7:30 o'clock. A moderate opacity surrounded the anterior Y suture, so that it stood out clearly. The anterior vitreous had a normal, clear anterior region and bulged forward between the lens and the edge of the iris. The vitreous was of average clearness. Retinoscopic study revealed two refractive systems, one phakic and the other aphakic.

III 27: E. G., a boy aged 9, when seen at the age of 8, was a healthy boy, whose only detectable abnormality was a left internal strabismus of 30 △. Refraction with atropine cycloplegia gave the following correction: right eye: +3.00 sph.⊃+1.00 cyl., axis 90, vision 6/10; left eye: +3.50 sph.⊃+1.00 cyl., axis 85, vision 16/200. No other ocular abnormality was noted.

In summary, this pedigree of three generations illustrates the hereditary nature of Marfan's syndrome. As shown on the pedigree chart, marriages between normal and affected persons resulted in 14 normal and 16 affected offspring. These figures must be accepted with certain reservations. Of the 16 persons, exclusive of the male progenitor of the line, who are described as having Marfan's disease, 5 exhibited the triad of arachnodactyly, dislocated lenses and indications of cardiac abnormalities; the disease in 9 members was characterized by only two aspects of the triad, while in 2 the diagnosis

rested on the finding of a single component of the triad. We have examined 10 of these 16 offspring. Possibly examination of the other 6 members of the family who were thought to have the disease would bring out other stigmas of the syndrome. In the 2 cases in which the diagnosis was made on the basis of a single finding, which in both was an ocular lesion, the diagnosis would be in considerable doubt were the cases isolated, and only the patients' position in the family and/or the defects in their children render the diagnosis of Marfan's disease probable. Of the 16 offspring of marriages between normal and affected persons who were classified as normal, 5 had either died so young that the disease might have been present and gone undiagnosed or were known to us only through sketchy statements. Some of these persons may have unreported signs of cardiac disease and minimal displacement or coloboma of the lens.

The difficulties which will always attend the diagnosis of Marfan's disease are well illustrated by this family. The classic case, such as that of *II 20, III 3, III 9, III 19 or III 26,* is unmistakable to one who bears the diagnosis in mind, but persons showing predominantly cardiac or only ocular abnormalities present serious problems of diagnosis, which may sometimes be resolved only by a careful study of parents, siblings, children or other relatives. *III 21* and *III 23* are excellent illustrations.

It is our impression that in this family, as well as in the cases reported in the literature, there exists all possible gradations from mild and scarcely recognizable Marfan's disease to the most extreme recorded picture. This is borne out by a study of table 2 and is of significance in connection with the genetic interpretation. Thus, in this pedigree the body configuration of affected persons range from the elongate, asthenic habitus of *II 20, III 9* (fig. 3*A* and *B*) and *III 19,* with slender extremities, thin stringy musculature and scarcity of subcutaneous fat, to the more normal build of *II 6, II 14* (fig. 2*A*), *III 4* and *III 21* (fig. 2*B*). Only 3 affected members were strikingly underweight, and 1 of these had advanced pulmonary tuberculosis when examined. Four of the remainder were essentially normal; 3 were slightly underweight, and 1 was obese. The twelfth person, a girl of 6 years, was so tall for her age that normal figures were not available for comparison. In all cases the arm span equaled or exceeded the height, but in no case did the span appear greatly out of proportion to the height, the greatest discrepancy being a span of 192 cm. in a 15 year old boy (*III 9*) 184.5 cm. in height. Measurements of the skull were obtained on 8 of the persons with Marfan's disease. In 7 instances a dolichocephalic or mesocephalic skull was observed, the

cephalic indexes ranging from 72.6 (*III 21*) to 78.8 (*II 14*). The single brachycephalic skull with a cephalic index of 85.2, occurred in a member (*III 9*) with the most extreme arachnodactyly. Many of the affected persons showed the well known hyperflexibility and motility of the joints, especially noticeable in the wrists and fingers. Weakness and relaxation of ligaments and muscles resulted in frequent pes planus, and there was inversion or eversion of the feet (especially in *III 3* and *III 9*). This, together with the elongate structure of the feet, with difficulty in obtaining proper footwear, made the feet a frequent cause of complaint. The terminal phalanx of the thumb and of the great toe often appeared enlarged, a feature which, with a second phalanx of smaller than average diameter, gave a clubbed appearance to these appendages. Cardiac signs varied from marked evidence of organic heart disease (*II 6, II 16, III 9* and *III 23*), through a mild murmur which may have been functional (*III 3* and *III 4*) to normal (*II 14, II 20, III 6* and *III 19*).

Clinically, the cardiac abnormality of several of these patients, as well as of the single member (*II 16*) on whom autopsy was performed, was regarded as rheumatic. Tobin, Bay and Humphreys [9] found cardiovascular abnormalities, including medial necrosis of the aorta and endocardial lesions simulating those of rheumatic fever, to be common in cases in Marfan's syndrome. In retrospect, the frequent evidence of cardiac defects within this family may have been on the basis of this disease, as well as on that of rheumatic fever. In the present state of knowledge, one cannot exclude the possibility that persons with Marfan's syndrome not only are apt to exhibit congenital cardiac abnormalities but are also susceptible to rheumatic fever or to pathologic processes the end results of which are indistinguishable from those of rheumatic fever.

The salient ocular characteristic of Marfan's syndrome is, of course, the ectopia lentis. Secondary to this is an iridodonesis over the aphakic area. Within this kinship, the presence of either various degrees of actual displacement of the lens or of a coloboma of the lens would appear largely dependent on the variations and the extent to which the zonular fibers were malformed. The zonular fibers hidden behind the iris were not visible for either examination or comparison with these in the aphakic area in any of the eyes, but the tendency throughout for the lens to be displaced, when this occurred, in an upward direction and for colobomas, when present, to be in the lower peripheral part of the lens suggests the probability of more nearly normal, or at least stronger, superior zonular fibers with the greatest

9. Tobin, J. R., Jr.; Bay, E. B., and Humphreys, E.: Marfan's Syndrome in the Adult, Arch. Int. Med. **8**:475 (Oct.) 1947.

developmental disturbance occurring in the embryonically less stable inferior region, corresponding to the fetal cleft.

The possibility cannot be finally ruled out, however, that some abnormality of the lens contributes to the dislocation and that the notching and rounding of the lens at the point of the coloboma represent not, as seems most probable, merely the reaction of the elastic lens capsule to deficient zonular fibers throughout the development of the lens but, rather, are due to an actual defect in the lens substance. For a discussion and a review of the various theories of the formation of coloboma of the lens and ectopia lentis, reference should be made to the treatises by Ida Mann,[10] Duke-Elder[11] and Bellows.[12]

Departures from the normal were observed both in the manner of attachment of the suspensory fibers, which were visible through dilated pupils, and in the structure of the individual fibers themselves. In some eyes there were areas along the periphery of the lens with complete absence of both the anterior and the posterior fibers, and with no evidence that any fibers had ever been present. In other regions, either the anterior (*III 26*) or only the posterior fibers were absent (*II 14, III 19*). In some eyes there was grouping of fibers, but with collections of broken fibers adjacent, as though only the "stronger" bundles remained (*III 9, III 26*). Marked variations in the caliber of the individual fibers within a single eye were observed (*III 9, III 19, III 26*). Correlated with these variations in the caliber and the distribution of the fibers were irregularities on the periphery of the lens. Thus, a series of small notches was present on the lens border in *III 9* and *III 19,* and in *III 26* the periphery was drawn into an angle by a group of heavy fibers. Inferiorly located colobomas of the lens were found in *II 20* and *III 23*. With few exceptions (*III 4, III 6, III 21*), in spite of the degree of displacement, the lenses appeared firmly anchored in position. In *III 6* and *III 9* the lenses may actually have been smaller than normal, and in *III 3, III 9, III 19* and *III 26* they may have been more spherical. Perhaps there is a relation between the unusual amount of trauma necessary to rupture these large zonular fibers within eyes of imperfect structure and the complication of retinal separation so frequently reported as a sequel to extraction of the lens in cases of Marfan's syndrome.

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10. Mann, I.: Developmental Abnormalities of the Eye, London, Cambridge University Press, 1937, p. 355.

11. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1349.

12. Bellows, J. G.: Cataract and Anomalies of the Lens, St. Louis, C. V. Mosby Company, 1944, p. 260.

There were other abnormalities in the eye. The anterior surface of the iris was lacking in the usual crypts and trabeculae. Theobald,[13] who examined histologically an eye from a child with arachnodactyly, found only rudimentary crypts of Fuchs on the iris. In 3 members of the present pedigree (*II 14, III 4 and III 21*) both pupils were oval, and in a fourth (*III 9*) the left pupil was eccentric. The pupils in *II 14* did not dilate beyond 5 mm. with paredrine® and homatropine. There were abnormalities in the distribution of the uveal pigment in all affected persons studied. The pupillary ruff was reduced in some instances (*III 4, III 19*). The peripheral portion of the iris could be transilluminated in all cases, but there was no evidence of coloboma. Theobold [13] noted a deficiency of pigment in a corresponding region. In the eye she examined histologically, the posterior layer of the pars iridica retinae was pigmented only over the pupillary half of the iris. The anterior vitreous possessed a normal appearance and bulged forward in the aphakic area in the majority of eyes, but was absent in *III 4, III 6* and *III 21*; the eyes of these 3 members showed the greatest disruption of the zonular fibers, pointing to an embryonic malformation common to both structures. In these 3 members, the aqueous was continuous with the posterior segment of the eye to such a depth that even at the deepest focus of the slit lamp only a few vitreous filaments were visible. Acquired alterations in the remaining zonular fibers of these eyes might lead to further displacement, or even complete loosening of the lens. Ophthalmoscopically, the vitreous of the left eye usually contained more opacities than that of the right eye.

Ten eyes were corrected through the aphakic area, and 6 through the phakic area (table 1). A double refractive system, one phakic, the other aphakic, each system correctable with lenses, occurred in the eyes of 2 members (*III 8* and *III 26*). The various degrees of myopia and myopic astigmatism appear to be largely lenticular. There was no relation between the degree of visual defect and the presence of an aphakic or a phakic system; even with the best lens correction, vision remained subnormal. In general, vision was better in the right eye than in the left eye. The anterior chambers were of average depth; when the lens was displaced backward, and over the aphakic area, the chamber was of greater than average depth. Tensions determined with the Schiøtz tonometer were normal both with dilated and with undilated pupils. Nystagmus (*III 6*), esotropia (*III 25*) and exotropia (*III 4*) occurred each in a single instance.

13. Theobald, G.: Post-Mortem Eye Examination, in Rambar, A. C., and Denenholz, E. J.: Arachnodactyly, J. Pediat. **15**:851 (Dec.) 1939; Histologic Study of an Eye from a Child with Arachnodactyly, Arch. Ophth. **24**:1046 (Nov.) 1940.

The color blindness present in 3 male members with Marfan's syndrome (*III 4, III 6* and *III 9*) was an independent occurrence, since none of the 4 female members with the syndrome who were tested showed defective color vision. The left prepapillary membrane observed in 2 women with the syndrome (*II 14* and *II 20*) was also present in 1 normal male member (*III 11*).

No operation had been performed on the eyes of any member of this family, and in no instance were significant cataracts observed; however, the oldest member living was only 49 years old. Bilateral amblyopia, found to be present without any correlation with the refractive error (table 1), is evidently part of the congenital syndrome; therefore, no appreciable improvement in visual acuity is to be expected from any surgical treatment. The defective vision was a handicap and probably contributed to the retardation in childhood noted in this family. For this reason, and as a measure to avoid an additional amblyopia ex anopsia being superimposed on the congenital defects, recognition of the condition in the eyes of persons with Marfan's syndrome at an early age is desirable, and a correction with glasses to the best possible vision is indicated.

On the assumption that all members of a sibship in which Marfan's syndrome is segregating have an equal chance of receiving hospital treatment when ill, there appears to be a strikingly greater tendency for those with the syndrome to attend hospital clinics than for their normal siblings, and this is not just a consequence of their ocular and cardiac disease. Rather, persons with Marfan's disease appeared to be especially susceptible to various acute infections, in particular to infections of the respiratory tract. Whether this is an anatomic consequence of their habitus or an expression of other, as yet unrecognized, factors cannot be stated.

GENETICS OF MARFAN'S SYNDROME

Marfan's original description [1] of the syndrome now associated with his name contained no reference to ocular abnormalities, nor did subsequent early reports recognize that the ocular defects which were sometimes observed were an integral part of the syndrome. It remained for Ormond and Williams [14] and Ormond [15] to focus attention on the frequent association of ectopia lentis and other ocular anomalies with arachnodactyly. Achard [16] was apparently the first

14. Ormond, A. W., and Williams, R. G.: A Case of Arachnodactyly with Special Reference to Ocular Symptoms, Guy's Hosp. Rep. **74**:385 (Oct.) 1924.

15. Ormond, A. W.: Etiology of Arachnodactyly, with Special Reference to Ocular Symptoms, Proc. Internat. Cong. Ophth. **2**:645, 1929.

16. Achard, M. C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834 (Oct. 10) 1902.

to report a familial incidence of the syndrome, the disease appearing in 2 sisters, their mother and the mother's father. Since then, a considerable number of family groups with two or more members presenting the full syndrome have been described, and there is general agreement among students of the disease that there are strong hereditary tendencies. To this day, however, it is not clear whether all cases of arachnodactyly represent the same developmental and genetic disturbance, with the absence of ocular anomalies in some pedigrees due to chance environmental and genetic modifiers, or whether there are several genetically distinct types of arachnodactyly, only one of which (but that the most frequent) is actually or potentially associated with ocular abnormalities.

Considerable differences of opinion have existed as to the exact nature of the hereditary factor or factors responsible for typical arachnodactyly. Frontali [17] suggested that the syndrome was due to a recessive factor, whereas Weve,[2] Killmann,[18] Apert [19] and Clement,[6] among others, stressed that the many pedigrees which have been described illustrated a dominant type of inheritance. Several of the clinicians who have studied Marfan's disease (Vogt [20]; Kurz [21]; Mann, in a personal communication quoted by Burch [3]; Ellis [22]; Rados [7]) have been unwilling to attribute so many apparently diverse effects to a single genetic factor, and so have postulated that the disease is due to a combination of two or more different, probably linked, dominant autosomal factors. A second fact leading them to this postulate was the apparent dissociation of ocular, skeletal and cardiac anomalies observed in some individuals in a pedigree. Thus, Rados,[7] suggesting the existence of a series of linearly arranged genes, each responsible for some aspect of the syndrome, wrote: "If there were a pluripotential gene common both for slenderness of the extremities and for luxation of the lenses, it would be impossible to understand why this combination should be present in some cases and absent in

17. Frontali, G.: Dolicostenomelia a carattere familiare in rapporto con zone di accrescimento osseo sopranumerarie, in Scritti medicci dedicati a Carlo Comba, 1929, p. 108.

18. Killmann: Angeborene doppelseitige Linsenektopie und Arachnodaktylie, Klin. Monatsbl. f. Augenh. **92**:335 (March) 1934.

19. Apert, E.: Les formes frustes du syndrome dolichosténomélique de Marfan, Nourisson **26**:1 (Jan.) 1938.

20. Vogt, A.: Arachnodactylie (Marfanscher Symptomen-Komplex) mit totaler Linsenluxation, Ztschr. f. Augenh. **75**:388 (Nov.) 1931.

21. Kurz, O.: Einige Fälle von Linsenektopie mit besonderer Berücksichtigung des konstitutionellen Moments, Klin. Monatsbl. f. Augenh. **92**:193 (Feb.) 1934.

22. Ellis, R. W. B.: Arachnodactyly and Ectopia Lentis in a Father and Daughter, Arch. Dis. Childhood **15**:267 (Dec.) 1940.

others" (page 489). Rados' review has had a wide influence on recent American students of the disease, and his views on the hereditary basis of the syndrome appear to be reflected in several publications of the past few years (Pasachoff, Madonick and Drayer [23]; Rosen [24]).

In our pedigree, the most extensive on record, the condition is transmitted as though due to one or more dominant autosomal factors. About half the offspring of marriages between normal and affected persons have themselves been affected. A final decision as to whether one, two or even three dominant genes are responsible for the production of the complete syndrome is impossible at present. It is quite possible, as previously suggested, that there are several genetic types. However, a number of considerations suggest that the simplest hypothesis, that of a single dominant gene, is the most probable explanation of the disease in at least the majority of pedigrees.

As was clearly pointed out by Apert,[19] the diversity of the manifestations of the syndrome does not constitute valid evidence against a unigenic hypothesis. Experiments with laboratory animals, such as Drosophila and mice, suggest that it is the rule rather than the exception for a single factor to have several phenotypic effects (Dobzhansky [25]). Grüneberg,[26] in his review of the genetics of the mouse, described a number of pleiotropic mutations in which the diversity of effects approximates that encountered in Marfan's syndrome (gray lethal, myencephalic blebs, shaker-short, short ear, macrocytic anemia, siderocyte anemia, kinky tail, Danforth's short tail). Neel [27] listed a number of mutations in Drosophila characterized by equally diverse effects (polymorph, spineless, aristopedia, Stubble, short wing, engrailed, ocelliless). Similar pleiotropic mutations have been described in rats and chickens.

Relatively little is known of the anatomy and physiology of mice and flies, as compared with knowledge of the human field. Furthermore, the detection of departures from the norm is more difficult in these small forms. If, notwithstanding, pleiotropy is the rule rather

23. Pasachoff, H. D.; Madonick, M. J., and Drayer, C.: Arachnodactyly in Four Siblings, with Pneumoencephalographic Observations of Two, Am. J. Dis. Child. **67**:201 (March) 1944.

24. Rosen, E.: An Atypical Case of Marfan's Syndrome, Am. J. Ophth. **28**:1134 (Oct.) 1945.

25. Dobzhansky, T.: Studies on Manifold Effect of Certain Genes in Drosophila Melanogaster, Ztschr. f. indukt. Abstammungs- u. Vererbungsl. **43**:330, 1927.

26. Grüneberg, H.: Genetics of the Mouse, London, Cambridge University Press, 1943, pp. xii and 412.

27. Neel, J. V.: The Polymorph Mutant of Drosophila Melanogaster, Am. Naturalist **76**:630 (Nov.) 1942.

than the exception in these animals, it is likely that pleiotropy prevails in man. The medical literature contains numerous examples of bizarre associations of anomalies in the appearance of which a hereditary factor is involved. These have recently been summarized by Gates.[28] It is of interest and significance that students of these various syndromes, when discussing the genetic background, have sometimes been reluctant, just as in Marfan's disease, to ascribe the multiplicity of effects to a single gene.

It is generally accepted that ectopia lentis may be inherited as a dominant trait in the absence of any skeletal defects (Kurz[21] Rados,[7] Falls and Cotterman,[29] Gates[28]). Likewise, pedigrees of dominant arachnodactyly without ocular defects have been reported, albeit rarely of late (Harrison and Klainer[30]). Little is known about the heredity of congenital heart disease. If the association of ocular, skeletal and cardiac defects seen in such families as the one reported here is due to the chance association of two or more genes on the same chromosome, then those postulated for "simple" arachnodactyly and "simple" ectopia lentis could be two of the genes in question. Unless linkage between the two genes is very close, one might logically expect to observe dissociation of the traits through crossing over. In this circumstance, a parent showing all the defects should produce some children showing only ocular or only skeletal or muscular defects. Such pedigrees have been reported. However, such a situation could also result if genetic and environmental modifiers acted on these children, to suppress some part of the syndrome (see next paragraph). The differential between these two possibilities is this: If crossing over is responsible for the dissociation, then in a pedigree of Marfan's disease a parent with ectopia lentis should produce children with this defect only, while the parent with skeletal and muscular defects should produce exclusively children with similar defects. However, Rados,[7] in his extensive review, cited several instances in which these conditions are not met, i. e., in which a parent showing only part of the syndrome produces children showing the full gamut of effects.[31] The pedigree we have described illustrates the same point (*II 6* and *III 9; II 14* and *III 19*).

28. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946, vol. 2, pp. xvi and 1518.

29. Falls, H. F., and Cotterman, C. W.: Genetic Studies on Ectopia Lentis, Arch. Ophth. **30**:610 (Nov.) 1943.

30. Harrison, J., and Klainer, M. J.: Arachnodactyly: Its Occurrence in Several Members of One Family, New England J. Med. **220**:621 (April 13) 1939.

31. Rados.[7] Such instances are to be found on page 486, line 23; page 495, line 38; page 496, lines 8, 11 and 14.

It is well known that genetic and environmental modifiers may powerfully influence the expression of various genes. The demonstration of genetic modifiers is difficult in man, where regulated matings are out of the question, since the detection of such modifiers depends on carefully controlled breeding experiments. However, there is ample precedent from comparative genetics for the existence of segregating modifiers whose effects are of sufficient magnitude to account for the differences between the forme fruste and the more extreme conditions. In the field of human heredity, wide variations in the expression of what is probably a unigenic trait have been described by many investigators, e. g., by Davenport and Muncey [32] for Huntington's chorea, by Mohr and Wriedt [33] for brachydactyly, by Falls and Cotterman [29] for ectopia lentis and by Lutman and Neel [34] for developmental cataract.

Finally, when one surveys the pedigree reported here, as well as the many recorded in the literature, one emerges with the impression that, so far as the "completeness" of the syndrome is concerned, there is a continuous spectrum ranging from the forme fruste to a condition much more extreme than that pictured in figure 3, with most cases occupying an intermediate position. There is no apparent tendency for a few chief types of Marfan's disease to emerge. The range in the ocular, skeletal and cardiac abnormalities, for example, is very wide, with most cases clustered about a centrally placed median. Such findings are to be expected when the action of a single "main" factor is subject to modification by other genetic and environmental determinants. One might expect a greater tendency to the occurrence of groups of similar cases if the findings were due to the interaction of only a few, incompletedly linked, factors.

To summarize, then, the data are, in our opinion, most consistent with the hypothesis that when Marfan's disease is present in a family it is probably due to a single dominant, autosomal, pleiotropic factor, the effects of which are sensitive to modification by other inherited, genetic modifiers, and perhaps factors in the early environment. It is possible that when this factor is introduced into a person whose genetic constitution is such that he would in the normal course of development evolve the asthenic habitus, typical Marfan's disease results. This

32. Davenport, C. B., and Muncey, E. B.: Huntington's Chorea in Relation to Heredity and Eugenics, Am. J. Insanity **73**:195 (Oct.) 1916.

33. Mohr, O., and Wriedt, C.: A New Type of Hereditary Brachyphalangy in Man, Publication 295, Carnegie Institute of Washington, 1919, pp. 64.

34. Lutman, F. C., and Neel, J. V.: Inherited Cataract in the B. Genealogy, Arch. Ophth. **33**:341 (May) 1945.

fact, as much as the existence of a forme fruste, may account for the apparently relatively frequent occurrence of asthenic members among the ascendants and collaterals of persons with Marfan's disease. In a person destined to be of the pyknic type, the introduction of the gene for Marfan's disease has less striking results, and the so-called forme fruste appears. In any event, the ocular anomalies may react to a different set of modifiers than the skeletal abnormalities. This concept of the importance of the "genetic milieu" in the expression of inherited traits, old in laboratory genetics, has not yet sufficiently permeated our thinking about human problems. That in an occasional case the disease may be due to a recessive factor cannot be ruled out, but the absence of a significant amount of consanguinity in the parents of affected persons suggests that this is not often true.

No family history of the disease is recorded in a high proportion of the cases in the literature. In view of the variability of the syndrome, caution must be exercised in accepting a case of Marfan's disease as "sporadic," in the absence of a medical and ophthalmologic examination of the patient's close relatives. Be that as it may, it seems likely that many, if not all, of the true "sporadic" cases have a genetic basis identical with that of the "inherited" form of the disease. Marfan's syndrome in its more extreme forms constitutes a serious threat to survival and reproduction. Natural selection must, therefore, be constantly tending to reduce the number of persons with this condition. Probably this fact, more than any other, accounts for the brevity of the published pedigrees of the disease. That the disease has not disappeared entirely must be attributed to the constant appearance through mutation of new cases, with the affected persons capable, if they survive and reproduce, of founding new pedigrees. Many, if not all, of the "sporadic" cases may therefore represent independent mutations of the gene responsible for the syndrome. Credit for first recognizing this possibility has been given to Bauer [35] by Rados [7] and Greiner and Varga,[36] although the references cited fail to bear this out. The validity of this assertion could be tested by studies of the offspring of persons with the "sporadic" form of twenty years ago, as pointed out by Rados [7] and Greiner and Varga.[36] The latter reported a "sporadic" case, in which there was no evidence of the

35. Bauer: 3 Säuglinge mit Wachstumsstörungen, Klin. Wchnschr. **6**:1117 (June 4) 1927; Demonstration dreier Säuglinge mit Wachstumsstörungen, Deutsche med. Wchnschr. **53**:1116 (June 24) 1927.

36. Greiner, K., and Varga, T.: Zur Aetiologie und Pathogenese der Arachnodaktylie, Ann. paediat. **164**:259 (May) 1945.

disease in any of the relatives, but in which it was transmitted to the patient's daughter, and pointed to this case as an example of the origin of a pedigree through mutation. Jequier [37] also stressed the possibility of such an origin.

In the case of a dominant trait such as this, if the population has reached an equilibrium between mutation and selection, so that the frequency of the disease is approximately constant over a number of generations, then, assuming that there is no overlap with the normal and that there is complete ascertainment of the syndrome in the population, the proportion of cases which are sporadic should equal the mean selective disadvantage of the disease. Of the 193 cases tabulated by Rados [7] with respect to the family history (table 5, after correction for error in column 1), 106 appeared to be "sporadic." All Rados' 7 certain cases, which were not included in this summary, were "sporadic." This proportion of "sporadic" cases, 50 to 60 per cent, is not unreasonable as an approximate index of the selective disadvantage of persons with the syndrome. Independent verification of this estimate might be derived from a comparison of the fertility of persons with arachnodactyly with the fertility of their siblings—unfortunately, the reports in the literature do not include this information. However, this figure can be accepted only as a rough approximation, since the species almost certainly is not at equilibrium with respect to the syndrome, diagnosis, especially of the milder forms of the disease, is far from complete and, as previously mentioned, the possibility of a recessive gene being responsible for an occasional case cannot be excluded. Persons with Marfan's disease are probably finding conditions increasingly to their liking in this era of good ophthalmology, sedentary occupations and decreased morbidity and mortality from pulmonary disease. For this reason, assuming that the mutation rate remains constant, the proportion of sporadic cases, even with allowance for failure to identify the disease in progenitors, should be in excess of the selective disadvantage, and the disease should increase in frequency.

It is of interest that a positive family history is most often elicited when the disease is mild. Thus, in a series of 193 tabulated cases, there was a positive family history in 69 of 164 typical cases, or 42 per cent, and in 18 of 29 atypical cases, or formes frustes, or 62 per cent. This suggests, of course, that patients with the milder forms of the disease manage to propagate more frequently than those with the severe forms, and so are more often characterized by a

37. Jequier, M.: Observations sur le syndrome de Marfan, Helvet. med. acta **10**:233, 1943.

positive family history. On the other hand, the fact that the sporadic cases tend to be more extreme gives further support to the mutation hypothesis of their origin. The findings in Marfan's disease tend to confirm a general principle in human inheritance which apparently was first brought out by Penrose [38] in connection with his studies on epiloia: "Sporadic" cases of a dominant abnormality tend to be severer than "inherited" cases, as persons who survive to reproduce will tend to carry genes diminishing the severity of the condition.

The disease is undoubtedly much commoner than the 200 or more described cases would indicate. From the broadly biologic standpoint, it is one of the most interesting diseases known to ophthalmologists. If the frequency of the syndrome could be established, an approximate estimate of the mutation rate would be feasible; from what little is now known, it appears that this mutation rate would be "high" by the standards used in judging mutation rates for Drosophila and corn. The detailed description of further extensive pedigrees is highly desirable. It is possible that the mutation process gives rise to a number of distinct alleles and that the relative mildness of the disease in this kinship is due to the occurrence of an allele with less pronounced effects than usual.

SUMMARY

1. In a kinship of 40 persons, 17 members probably had Marfan's syndrome (arachnodactyly, ectopic lentis, indications of cardiac abnormalities and other congenital defects).

2. There was a great variability in the expression of the syndrome in the affected members of the kinship. In addition to classic cases, there existed in this family members so mildly affected that the diagnosis would be unsuspected or in doubt were it not for their genetic background.

3. Ocular anomalies observed in all persons studied, in addition to either ectopia lentis or coloboma of the lens, were abnormal zonular fibers, an iris lacking in the usual surface trabeculae and crypts, deficiencies of uveal pigment, particularly at the periphery of the iris, and amblyopia. In several cases these were accompanied with other ocular defects.

4. The syndrome is inherited as though due to one or more dominant autosomal genes. Although a final decision is not possible, the bulk of the evidence suggests that the entire syndrome may be due to one gene only whose expresssion is greatly influenced by other genetic, and possibly by environmental, factors.

38. Penrose, L. S.: Autosomal Mutation and Modification in Man with Special Reference to Mental Defect, Ann. Eugenics **7**:1 (June) 1936.

5. In view of the threat to survival and reproduction imposed by Marfan's disease, it is felt that the syndrome would quickly disappear through natural selection unless there were a relatively high mutation rate from normal to the gene responsible for this syndrome. The many isolated cases which have been reported are thought for the most part to represent the results of this mutation process.

Mrs. T. Sample and Mrs. G. P. Moody, of the Eye Clinic, and Miss E. C. Baker, of the Social Service Department, assisted in this study.

MORPHOLOGIC CHANGES IN CELLS OF CORNEAL EPITHELIUM IN WOUND HEALING

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THE IMPORTANCE of epithelial cell movements as a primary phenomenon in epithelial wound repair may be considered as well established by the work of Peters, Arey and others.[1] In regard to the mechanism of these movements, it is of interest to know whether the epithelial cells move individually or en masse, i. e., as a continuous epithelial sheet.

Observations on healing phenomena in amphibian embryos suggested that in the healing process of epithelial injuries the continuity of surface coats of tissue plays an important role.[2] Movement of epithelium en masse as a possible mode of epithelial wound repair seems to be illustrated by observations on the displacement of the limbal pigment line and of conjunctival goblet cells onto the cornea in the epithelial repair of burns of the cornea due to mustard gas (*2*-chloroethyl sulfide).[3] Observations on the healing of mechanically produced epithelial defects in the rat cornea[4] revealed striking differences in the orientation of the epithelial cells, dependent on the size and shape of the injury: With small injuries, the surrounding epithelial cells became radially oriented

From the Ayer Foundation Ophthalmic Research Laboratory, Manhattan Eye, Ear and Throat Hospital.

This work was reported in part at the Fifty-Seventh Annual Meeting of the American Physiological Society, Atlantic City, N. J., March 18, 1948 (Federation Proc. **7**:17, 1948).

1. Literature on the subject may be found in recent reviews: (*a*) Buschke, W.: Experimentelle Studien zur Patho-Physiologie des Hornhautepithels: Zell-Bewegungen bei der Wundheilung, Zellteilung, Mitosehemmung und andere Kernphaenomene, Ophthalmologica, in Festschrift für Brueckner, to be published. (*b*) Friedenwald, J. S.: Studies on the Healing of Corneal Wounds, in Wiener, M.: Ophthalmology in the War Years, Chicago, The Year Book Publishers, Inc., vol. 2, to be published.

2. Holtfreter, J.: Properties and Functions of the Surface Coat in Amphibian Embryos, J. Exper. Zool. **93**:251, 1943.

3. Maumenee, A. E., and Scholz, R. O.: Histopathology of the Ocular Lesions Produced by the Sulfur and Nitrogen Mustards, Bull. Johns Hopkins Hosp. **82**:121, 1948.

4. Buschke, W.: Further Observations on Epithelial Movements in Wound-Healing, Federation Proc. **6**:85, 1947.

during the healing process, in the manner described previously [5] as typical of the healing of pinprick injuries; with larger injuries or linear lesions, on the other hand, the cells adjoining the injury became tangentially oriented and were found in this orientation for several hours after injury. Detailed observations on the fate of the individual cells near the margin of the wound appeared desirable.

The relatively small diameter of the epithelial cells in the rat cornea (8 to 10 microns) and the large number of epithelial layers made it difficult in this species to observe details of the cell outlines in flat preparations; on the other hand, the use of flat preparations was the technic offering the most promise in establishing histologic details of the relation of individual cells to each other, eliminating the cumbersome methods of reconstructing a synoptic picture from serial sections. Use of frog corneas with only three layers of epithelium, with cells having

Data on Epithelial Movements in Wound Healing of the Cornea

	Duration of Lag Period of 1 Hour at	Temperature Coefficient (Q_{10}) $\left[\text{Log } Q_{10} = \frac{10(\log k_1 - \log k_2)}{t_1 - t_2}\right]$	Approximate Temperature Range of Q^{10} in column 2, Degrees (C.)	Loosening of Epithelial Sheet with 3 Hours' Incubation in Moist Chamber
Frog.....	20 C.	3 ±	5 - 25 C.	30 C.
Rat.....	37 C.	5 ±	15 - 40 C.	45 C.

a diameter of 12 to 15 microns, promised to facilitate detailed observations. Ameboid cell movements in epithelial wound repair of partially denuded frog corneas were reported as early as 1885.[6]

METHODS AND PRELIMINARY EXPERIMENTS

The frogs used in this study were adult specimens of Rana pipiens from Vermont which were kept with running water in the laboratory. Experiments were carried out between September 1947 and March 1948.

Pinprick wounds of the corneal epithelium of the frog were made and the injuries studied in flat preparations at various intervals thereafter with the methods and technics described previously for the rat.[5] After injury, either the eyes were left in the animal for the time interval to be studied, or they were removed immediately and kept in vitro in moist chambers for a period before fixation. Linear lesions were produced by scratching with a needle. Large lesions were produced either by denudation of one half of the cornea with a scalpel or, for crushing injuries, by slow torsional movements of a small carborundum drill operating under moderate pressure.

5. Friedenwald, J. S., and Buschke, W.: Influence of Some Experimental Variables on the Epithelial Movements in the Healing of Corneal Wounds, J. Cell. & Comp. Physiol. **23**:95, 1944.

6. Peters, A.: Regeneration des Epithels der Cornea, Inaug. Dissert., Bonn., 1885.

In preliminary experiments, the time and temperature relations of the healing process in pinprick injuries were first to be determined for the frog. The results as compared with those for the rat are summarized in the accompanying table. At appropriate temperatures, the latent period between time of injury and onset of cell orientation was found similar to that in the rat. If one considers a temperature of about 37 C, as an approximately physiologic temperature for the rat cornea, a similar latent period of one hour was found to exist for the frog at about 20 C. Like the rat, this latent period was inversely related to temperature, with a temperature coefficient of 3, i.e., a value lower than that for the rat, but still of such magnitude as to signify the importance of energy-requiring processes during this period of lag.

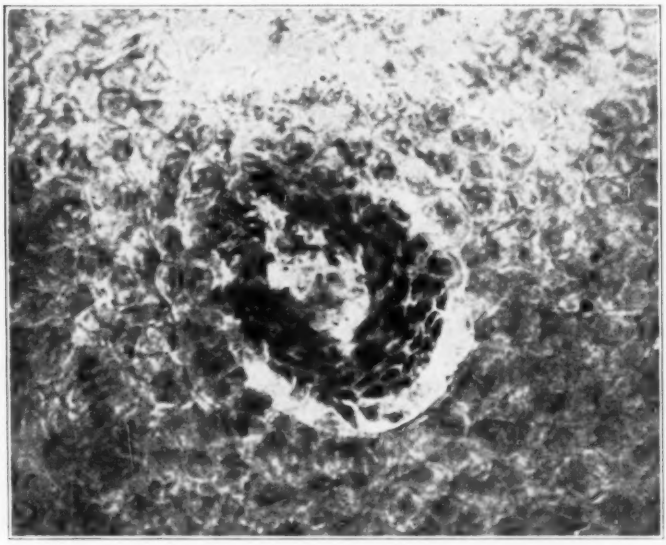

Fig. 1.—Sequestration of central plug of damaged cells and sealing off of wound margin in superficial epithelial layers of healing pinprick injury. Frog's eye; moist chamber; two hours; 24 C.; 280 × linear.

MORPHOLOGIC OBSERVATIONS

Pinprick Injuries.—During the period of lag between injury and onset of cell orientation, the centrally located, most severely damaged cells became separated from the more peripheral ones, and this central plug eventually became completely sequestrated and sloughed: This sloughing apparently takes place spontaneously in experiments in vivo, while it may occur in the fixative in the in vitro experiments. During or near the end of this process, the adjoining cells of the epithelial sheet

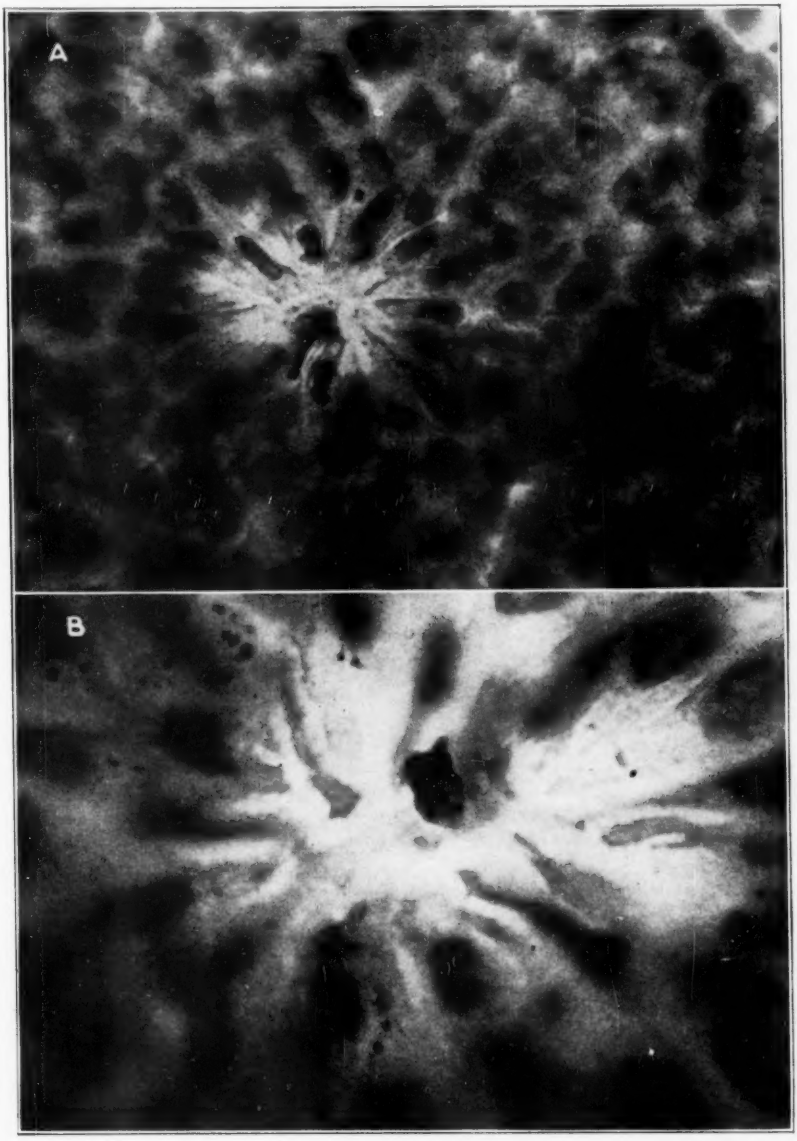

Fig. 2.—Pseudopodial movements of basal epithelial cells in healing pinprick wound. Frog's eye; moist chamber; two and one-half hours; 17 C. *A*, 850 ×, *B*, 1,890 × linear.

became oriented in a manner which depended characteristically on the layer in which the individual cell was located. The cells in the superficial layers became oriented tangentially toward the injury with the nuclei and cell bodies flattened, thus forming a microscopically continuous surface which sealed off the rest of the epithelial sheet from the central plug (fig. 1).

Application of silver stain to corneas during the latent period according to the technics described previously [7] showed that the central plug was strongly stainable with silver.

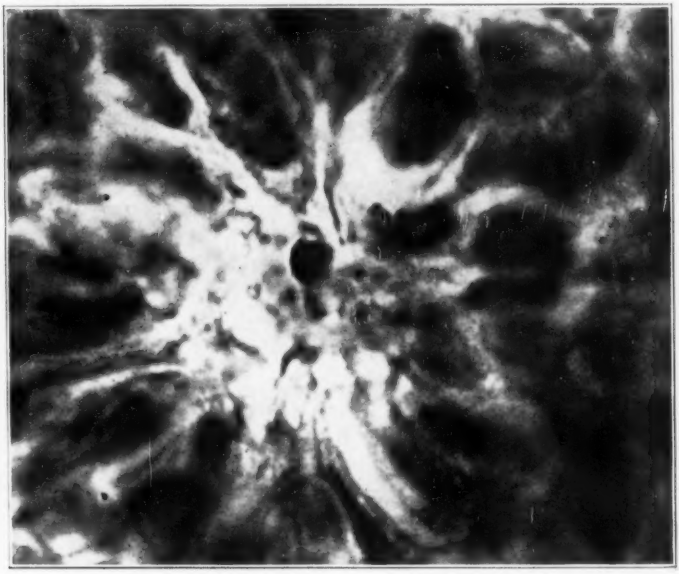

Fig. 3.—Pseudopodia of neighboring and opposing epithelial cells making contact in central denuded area in later stage of healing of pinprick wound. Frog's eye; moist chamber; two and one-half hours; 24 C.; 1,190 × linear.

At places where, or at a time when, the basal layers were no longer covered by the central plug, details of the basal epithelial cells could be seen; these cells, which were beginning to rearrange themselves radially after about three-fourths to one hour at a temperature of 20 C., showed many pseudopodial extensions directed toward the area of the defect.

7. Friedenwald, J. S.; Buschke, W., and Crowell, J. E.: Exudate from Injured Cells and Its Relation to the Healing of Wounds of the Corneal Epithelium, J. Cell. & Comp. Physiol. **25**:45, 1945.

Sometimes these extensions of the cell surface and cytoplasm were of considerable length, and usually the cell nucleus assumed shapes which corresponded roughly to that of the whole cell. Occasionally, also, cells of the second column behind the margin of the wound extended long pseudopodia into the denuded area, and these pseudopodia were obviously squeezing themselves through narrow spaces between two neighboring

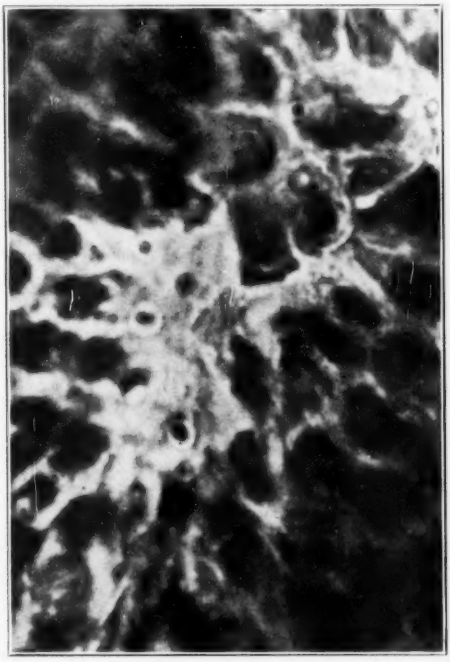

Fig. 4.—Pseudopodia in healing of pinprick wound in rat's corneal epithelium. Moist chamber; two hours; 37 C.; 1,190 × linear. For preliminary treatment, see text.

cells of the first column. In many cases the peripheral cells showing ameboid response had lost morphologically recognizable contact with neighboring cells for some parts of their cell surface (fig. 2). In later stages in the healing process of pinprick injuries, i.e., after two to three hours, the surfaces of the pseudopods of several neighboring or opposing cells made contact with each other, thus leading to a picture which began to resemble the normal continuity of the epithelial sheet (fig. 3).

While these details were clearly observable in the frog cornea in either hematoxylin-stained or unstained flat preparations, the thickness of the epithelium and of the centrally located damaged cells made it

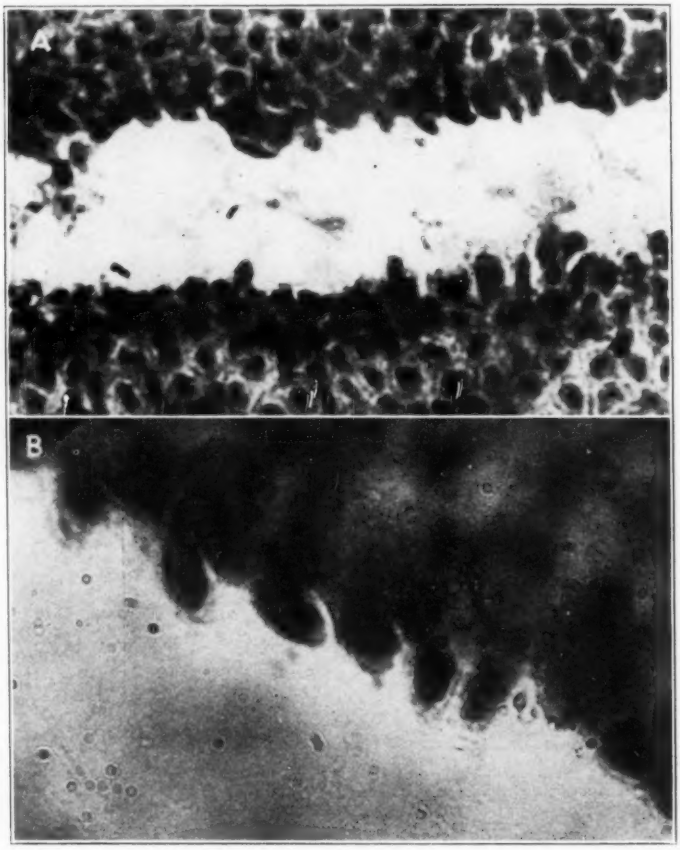

Fig. 5.—Rugged outlines of wound margin in fresh needle scratch. Frog's eye; (*A*) 300 × linear; (*B*) 910 × linear.

difficult to observe similar details in rat corneas with the standard technics. Recently, however, we have been able to make similar observations in rats under more favorable optical conditions. If corneas or whole eyes were stored in vitro in a moist chamber, the epithelial nuclei

lost their stainability with basic dyes, without any significant changes in the normally existing slight stainability of the cytoplasm and of the cell surfaces. This loss of stainability occurred at temperatures and with a duration of storage at which no interference with the wound healing movements of the epithelium was observable. It thus became possible, under appropriate conditions, to see details of the

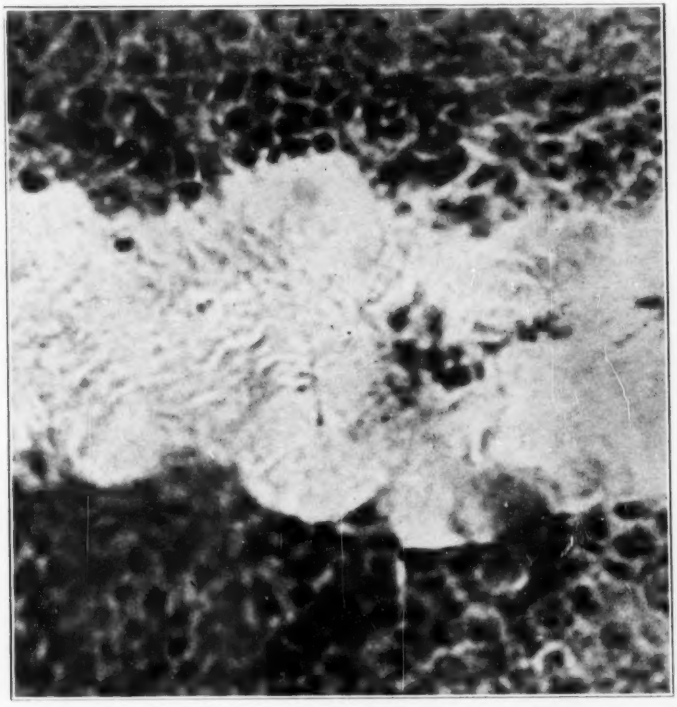

Fig. 6.—Smooth, sealed-off wound margins, with arcades, forty minutes after injury due to needle scratch injury. Frog's eye; moist chamber; 24 C.; 300 × linear.

cellular outline better than in either unstained or freshly stained preparations. Experiments were arranged as follows: Rat eyes were stored in moist chambers for twenty-four hours at 18 C. Pinprick injuries were then made in the corneal epithelium and the eyes stored at 37 C. for an additional period of two hours. The eyes were then fixed, and flat preparations of the corneas were made and stained with

hematoxylin diluted 1:18, as usual. Figure 4 shows the appearance of the cells surrounding a pinprick injury after two hours of secondary storage following the injury. Pseudopodial extensions can be seen in several of the adjoining cells, and, although these pseudopods are shorter than many of those which had been seen in frog corneas, the phenomenon is very similar to that in the frog.

Linear and Larger Injuries.—In contrast to the radial orientation in the early stages of the healing of pinprick injuries, the epithelial cells adjoining either linear lesions (needle scratches) or larger injuries showed a morphologically different response. As a rule, the outline

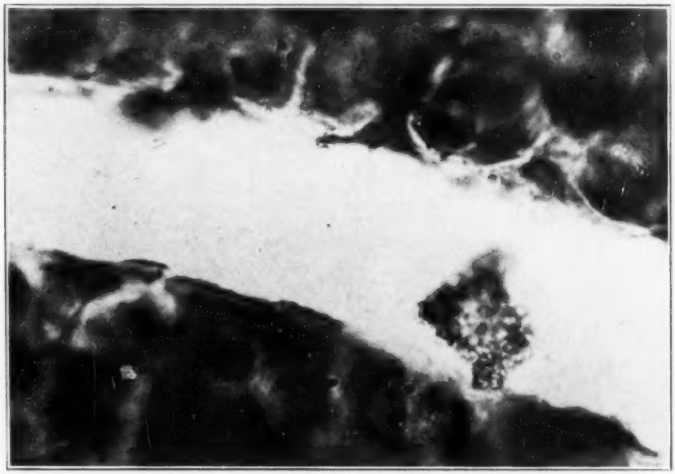

Fig. 7.—Mushroom-like spreading and flattening of epithelial cells at wound margin of linear lesion, sixty minutes after needle scratch. Frog's eye; moist chamber; 24 *C.*; 778 × linear.

of the epithelial sheet in those injuries was rugged in preparations which were fixed immediately after injury (fig. 5). After a latent period similar to that leading to radial orientation of the cells in pinprick injuries, the wound margins of linear and larger lesions became smooth, and often assumed an arcade-like shape (fig. 6). The morphologic changes of the cells which led to this appearance consisted in a mushroom-like spreading and flattening of the marginal cells, which sealed off the epithelial sheet with a microscopically more or less continuous surface toward the denuded area (fig. 7). This appearance was maintained for many hours; pseudopods extending into the denuded

area, familiar now from the healing of pinprick injuries, were at first seen chiefly in places where the wound margin of the epithelial sheet showed smaller pockets (fig. 8).

COMMENT AND SUMMARY

Differences in cell orientation in the healing process depend on the size and shape of the injury, as well as on the layer of the epithelial sheet in which the responding cells are located.

Fig. 8.—Healing of large erosion, showing smooth outlines of wound margin for long stretches and pseudopodia in smaller pocket of wound margin. Frog's eye; moist chamber; twenty hours; 24 C.; 345 × linear.

1. Pseudopodial extensions of the cytoplasm directed into the denuded area are seen in the basal layers of the epithelium in the early stages of healing of pinprick injuries, these pseudopods being observed particularly in pockets of the wound margin in the healing of larger injuries.

2. Spreading and flattening of the epithelial cells, leading to sealing off of the wound margin, are seen in linear and larger lesions in the

early stages. This sealing off is seen also in the healing of small injuries in the superficial layers of the epithelium.

At present, no proof is available for any theory which would explain these differences in morphologic response. However, several possibilities may be discussed. One possibility is that of a difference in the amount of damaged cells and extracellular material present in the wound zone. It is in the nature of the technics used in the production of these various injuries that the amount of damaged and disintegrating cells in the injured zone is larger in pinprick wounds than it is in needle scratches or in larger erosions produced with a scalpel. However, in experiments with larger injuries, where large portions of the epithelium were crushed by drill-like torsional movements of a dull instrument, the response was essentially that observed in other large injuries. Furthermore, in pinprick wounds the superficial layers of cells responded morphologically in a different way than did the basal layers, in spite of the presence of the central plug of disintegrating cells. An alternative explanation, therefore, may be considered more likely, namely, that intrinsic properties of the epithelium are responsible for differences in morphologic response. It may be suggested, for example, that movement of individual cells is a resultant of forces acting on the free surfaces of individual cells, on the one hand, and of forces acting on the continuum of the epithelial sheet at and near the wound margin, on the other. In this case the morphologic response of the individual cell may be expected to vary (*a*) with the degree to which a continuity exists in the epithelial sheet surrounding the wound zone, and this may differ in different layers of the epithelium, and (*b*) with the curvature of the exposed wound margin and, as a function of this curvature, with the number of exposed cells at the wound margin in relation to its surface area. While such an explanation is as yet unproved, it represents a working hypothesis, in which the continuity of the epithelial sheet surrounding the wound zone is a potential variable affecting the movements of wound healing, and variables affecting the intercellular cohesiveness of the tissue are determining factors, in addition to direct or indirect stimuli issuing from the injury itself.

This study was carried out with the technical assistance of Miss Margaret White. The photographs were made by Mr. Don Allen, photographic laboratory, Manhattan Eye, Ear and Throat Hospital.

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MYXOSARCOMA OF THE EYELID

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PRIMARY sarcomas of the eyelids are of comparatively rare occurrence. Although several types have been recognized, a certain amount of confusion has resulted from efforts to draw an exact histologic delineation. Various types of tissue and cell formation are consistently present in one tumor, some of which can be only imperfectly differentiated. Reference in the literature to malignant growths of the eyelids exhibiting myxosarcomatous elements are infrequent; that of van Duyse and Cruyl [1] is typical.

These authors reported the case of a girl 7 years of age who had been struck by a rope nine weeks prior to her admission to the hospital, on July 23, 1887. A week after the blow had been received, a small tumor, resembling a chalazion, was noted on the left upper eyelid. For a week the growth remained quiescent and then enlarged rapidly. Four days after hospitalization, during which time further growth was apparent, an operation for removal of the tumor was performed. The point of origin appeared to be in the loose cellular tissue separating the tarsus from the orbicular muscle. The growth was approximately 20 cm. at the base, was situated under the skin of the eyelid and had ballooned the conjunctiva into a sac which covered more than half the cheek. In a later article, van Duyse [2] reported a recurrence of the tumor, which necessitated removal of the entire eyelid three months after the first operation. A further recurrence involved the entire orbital cavity together with an external growth the size of the child's head; operation was performed on July 22, 1888, and the patient died in less than a month.

The microscopic examination of the original growth showed that portions of the section stained uniformly and had the appearance of fully developed tissue; these areas predominated. Fusocellular elements surrounded the vessels and filled the intervascular spaces. In these spaces, which were characterized by an abundance of mucous tissue,

1. van Duyse and Cruyl: Myxosarcome de la paupière supérieure; sarcomes de la conjonctive palpébrale; remarques sur les tumeurs sarcometenses de la paupière et de la conjonctive palpébrale, Ann. d'ocul. **98**:112, 1887.

2. van Duyse: Sarcome de la paupière, Ann. d'ocul. **101**:227, 1889.

the clearly disseminated embryonic element was the dominant form. The myomatous aspect appeared secondary. The presence of fine fat droplets was explained by the similarity in the fundamental substance. In other areas the myxomatous aspect was replaced by a tissue composed of small fusiform cells; this pure sarcomatous tissue was predominant. In many places the capillary vessels were conspicuously dilated; in others there was a true cavernous circulation (cavernous sarcoma, not angiosarcoma). No myeloplexes or hyaline degeneration of the vascular walls was observed. The diagnosis was myosarcoma.

The French authors cited Ziegler,[3] who stated:

> The tumors in which sarcomatous and mucous tissue are found combined have, on section, either a hyaline or an opaque, dirty white appearance. The mucous tissue is partly composed of a network of ramified and anastomosing cells in addition to a mucoid basis-substance. Within this tissue lie, also, branching clumps and strings made up of closely-compacted cells. These strings are very irregular in form and anastomose in all directions; they give the tumor a very peculiar texture. Its general structure justifies the name myxosarcoma.

Flack[4] reported a case of sarcoma affecting the right eyelid in a girl aged 9. The tumor was primarily a spindle cell sarcoma but contained areas of fat and of myxomatous tissue. The author appended a résumé of recorded cases, in 3 of which the tumor was a myxosarcoma. A year later, Wilmer[5] removed what he termed a "melanotic giant-celled, alveolar, myxo-sarcoma" from a woman aged 30. The growth had been noted for the first time eight months previously, but no associated trauma was remembered by the patient. Microscopic examination of the tumor showed a framework of wavy bands of dense fibrous connective tissue running in all directions, through which small dense black masses of pigment were irregularly distributed. Numerous islands of myxomatous tissue, surrounded by alveoli of dense fibrous connective tissue, were composed mostly of round cells, with some spindle and stellate cells.

On Oct. 4, 1906, Alling[6] removed a primary tumor and several smaller growths from the lower eyelid of a girl aged 7 years. The growth was of six weeks' duration; the patient was healthy and gave no history of trauma. By the middle of December a recurrence of a malignant nature was present; this affected both lids and necessitated a

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3. Ziegler, E.: A Text-Book of General Pathological Anatomy and Pathogenesis, translated by D. MacAlister, New York, W. Wood & Co., 1883, p. 227.

4. Flack, J.: Ueber Sarkome der Augenlider, Koenigsberg, M. Liedtke, 1892.

5. Wilmer, W. H.: A Case of Melanotic Giant-Celled, Alveolar, Myxo-Sarcoma of the Eyelid, Tr. Am. Ophth. Soc. **7**:91, 1894-1896.

6. Alling, A. N.: Primary Sarcoma of the Eyelid, Ophth. Rec. **16**:282, 1907.

more radical operation, which was performed Jan. 1, 1907. At that time the outer half of the lower lid was removed and extensive dissection of the upper lid was carried out. The child died of scarlet fever while still in the hospital. Microscopic examination revealed a tumor of mixed character: What appeared to be strands of fibrous tissue were interspersed with cell masses, intercellular substance and thin-walled blood vessels. The intercellular substance was somewhat granular and stained like mucoid tissue. The cells were small and irregular in shape and showed numerous mitoses. The diagnosis was fibromyxosarcoma.

Alling mentioned primary sarcoma of the eyelid as among the most uncommon of ocular lesions. As a rule, this tumor develops in previously normal tissue and occurs more frequently in youth than in old age. The growth appears to originate from a contusion, a point emphasized by de Schweinitz.[7] The melanotic type especially may be secondary to a wart or nevus. Melanosarcoma is the most frequently observed type of malignant tumor; myxosarcoma is seen least often. A study of primary cell structure showed 34 per cent of the spindle cell type, 32 per cent of the round cell type and 26 per cent of the mixed cell type. These tumors are characterized chiefly by their rapid growth, early recurrence and high percentage of fatalities.

REPORT OF A CASE

L. F., a 9-year old white boy, was seen at the ophthalmic clinic on May 27, 1941, with a swelling of the left upper eyelid. The patient's mother stated that the boy had been hit in the eye with a ball during the last week of April of that year. However, neither edema nor ecchymosis was evident until May 10, when a swelling as large as a cherry was noted on the upper lid. The lesion increased rapidly in size, was fluctuant and resembled a hematoma. At the time of examination, the patient had 20/30 vision in the right eye but could not raise the left eyelid. The veins in the lid were dilated; the tissue of the fornix was depressed, and the globe was somewhat injected but not displaced. One cubic centimeter of bloody fluid was obtained by diagnostic puncture. The patient's family and past history were not contributory. The swelling became more pronounced, and the boy was admitted to the hospital four days later (fig. 1).

Roentgenographic studies of the entire skull were made on May 31 and June 3 from positions so chosen that the soft tissue lesion was not a hindrance. The reports indicated no abnormality of the sinuses and no evidence of fracture or disease process of the bone. Neurologic examinations, one made on June 3 and a second one week later, failed to reveal any material change in the clinical picture. Nothing was found to indicate intracranial disease, and neither the central nervous system nor the meninges appeared to be involved. The diagnostic possibilities of cellulitis, abscess and thrombophlebitis of the cavernous sinus were discarded, owing to the abscence of characteristic systemic reactions

7. de Schweinitz, G. E.: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1924, p. 188.

or positive intranasal findings. Interference with the venous drainage from the orbital region was noted. The possibility of a rapidly growing tumor was discussed and, with the uncertainty of the diagnosis in mind, high voltage roentgen therapy over the left orbit was suggested.

Permission to operate was obtained, and on June 5, with the child under ether anesthesia, an incision 8 cm. in length was made in the skin just above the supraorbital margin. A deep pocket in the lid was entered with a hemostat. A few blood clots were present, but no pus was evacuated. A drain was inserted and a pressure bandage applied. On June 7 additional drainage was considered advisable. With the use of ethyl chloride and ether, two incisions were made in the conjunctiva, and two rubber drains were passed through them and through the original wound above. Two further incisions were made in the skin of the upper lid. Drains were placed without any obstruction being encountered.

FIG. 1.—The tumor, with drains inserted.

Irradiation was carried out on June 13 and 18. A dose of 100 kilovolts and 3 milliamperes was delivered at a target-skin distance of 40 cm. with a 2 mm. aluminum filter for one minute during the first treatment and the same amount for two minutes during the second.

On June 3 and 21, respectively, the hematologic findings were as follows: red cell count, 5,110,000 and 4,360,000; white cells, 12,200 and 6,250; polymorphonuclear leukocytes, 69 and 57 per cent; lymphocytes, 28 and 40 per cent; eosinophils, 1 and 3 per cent; hemoglobin, 96 and 84 per cent. On June 13 both the coagulation and the bleeding time were two minutes. Other laboratory findings were not significant.

For three weeks, the boy's parents were unwilling that further surgical procedures should be carried out. During that time the patient remained alert and active, but the nature of the lesion changed from a soft, hematoma-like structure to a firm mass. There was some healing of the incisions, and a slight

mucopurulent discharge was present, but no bleeding. Sulfathiazole, 5 per cent, and azosulfamide, 5 per cent, were applied locally. On June 28 an operation was performed, with the patient under ether anesthesia. A horizontal incision was made in the skin of the left eyelid midway between the lid margin and the

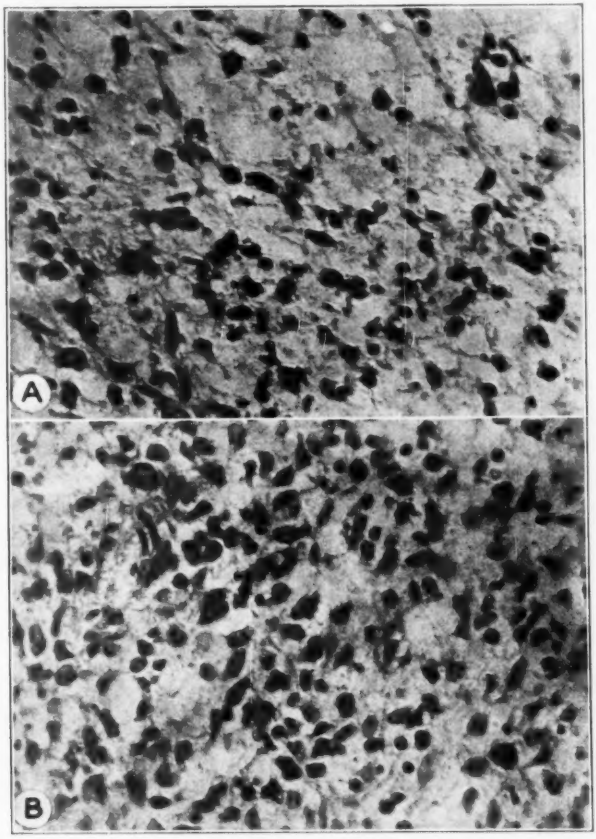

FIG. 2.—Sections from the excised tumor, characterized by pronounced variation in cell structure, numerous mitotic figures and hyperchromatic nuclei. *(A)* The loose cellular structure shows an abundant clear mucoid matrix. *(B)* A more cellular area shows the variation in cell structure. Staining properties of the nuclei indicate the anaplastic character of the tumor and its rapid rate of growth.

brow line. Immediately beneath the derma a mass was encountered, which, when separated from the lid, was found to extend back into the socket. There

was considerable bleeding. A portion of the tumor, which equaled a golf ball in size, was excised and the remainder curetted.

Grossly, the tumor was friable and semitranslucent and had the appearance of fish flesh. Microscopically, spindle cells of anaplastic type in a loose myxoid matrix were observed. The vascularity was extensive, and focally there was a peritheliomatous arrangement of the tumor cells. The pathologic diagnosis was myxosarcoma of the left eyelid and orbit (fig. 2).

On July 3, 1941 the patient was transferred to the Brooklyn Cancer Institute, where he remained until July 22. A cycle of roentgen treatments was instituted on July 11 and completed on August 1.[8] Three portals, 6 by 8 cm., were used: one supraorbital, with the rays directed downward through the eyeball; one anterior and one left lateral. A dose of 200 r was delivered to each of two areas. A total of 2,000 r was delivered to each portal, the dose received by

FIG. 3.—Photograph of the patient, taken in 1948, showing the retracted socket and retained eyelids, with only minimal scarring. A plastic reconstruction of the orbital socket to receive a prosthesis will be made.

the tumor within the center of the orbit during this twenty-one day interval being estimated as 6,000 r. As a result of this rather intensive treatment, the tumor subsided to a large degree.

The boy's condition was subsequently followed through the outpatient department. In April 1943, the skin of the left lid showed marked depigmentation; the conjunctiva of the eye was engorged; there were photophobic lacrimation and discharge, vascularization of the cornea and changes in the lens. This clinical picture was believed to be secondary to the radiation therapy. Examination eighteen months later revealed advanced phthisis bulbi and entropion. When the patient was observed on Jan. 7, 1946, a generalized symblepharon of the shrunken eye, with considerable crust formation over the cornea, was present.

8. The information regarding the course of treatment at the Brooklyn Cancer Institute was received in a personal communication from Dr. Benjamin C. Rosenthal.

The photophobic lacrimation and general irritability of the eye were more intense, and the possibility of perforation of the globe was considered.

On January 26, enucleation was performed, with the patient under general anesthesia. Examination of the cornea after removal of the crust revealed no evidence of perforation. Both lids were adherent to the cornea; the conjunctival cul-de-sacs were completely obliterated, and considerable scar tissue was present in the entire orbital region. After removal of the eye, tissue from the deep areas of the walls, roof and floor of the orbit was sent to the laboratory. The pathologist's report on each section was, "Normal tissue; no tumor found."

The patient's recovery was uneventful, and he left the hospital on Feb. 1, 1946, although dressings were continued and the condition was watched at office visits. By December 1946, the socket had contracted completely, the lids were retracted by scar tissue and there was no discharge from the area (fig. 3).

SUMMARY

This case represents an example of myxosarcoma of the eyelid apparently resulting from trauma. There was no evidence of injury prior to or until two weeks following the accident; then a lesion appeared on the upper lid and enlarged rapidly. The growth resembled a hematoma but changed within two months to a firm, unyielding mass. Partial resection of the tumor and radiation therapy were employed. The eye was removed two years after the operation. Biopsy specimens from the surrounding areas showed no residual tumor, and no evidence of metastasis has been found. The boy is in good health; he has developed normally and presents no defects other than the loss of one eye. At present, nearly seven years after the appearance of the initial lesion, there is no reason to suspect a recurrence of the malignant growth.

15 Schermerhorn Street.

MOTAIS-PARINAUD TYPE OF OPERATION FOR PTOSIS

Report on Thirty-Five Cases

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EVER since, forty years ago, Motais [1] and Parinaud [2] simultaneously described an operation for correction of ptosis by suspending the tarsus of the upper lid from the superior rectus muscle, this type of operation has been repeatedly revived, with modifications.

Motais originally exposed the superior rectus muscle and the anterior surface of the tarsus through a conjunctival incision and then fashioned a flap from the middle third of the superior rectus muscle, which he sutured to the anterior surface of the tarsus. To simplify the technic of the operation, Shoemaker [3] and Taggart [4] made incisions through the skin, as well as through the conjunctiva; and later Kirby [5] performed the operation entirely through the skin. This small muscle flap often pulled away, resulting in failure. In other cases, in which the muscle flap did not slip, an exaggerated Gothic type of arch developed, deforming the normal curve of the lid. To prevent the flap from pulling away, Morgan [6] and Ellett [7] suggested excising a small piece of sclera with the muscle flap. To avoid creating an inverted V type of curve of the upper lid, Stephenson [8] advocated using the outer third of the superior rectus muscle, whereas Duverger and Velter [9] proposed using the inner half.

From the Institute of Ophthalmology of the Presbyterian Hospital of the city of New York.

1. Motais, M.: Operation du ptosis par la greefe tarsienne d'une languette due tendon du muscle droit supérieur, Ann. d'ocul. **118**:5, 1897.

2. Parinaud, H.: Noveau procédé operation du ptosis, Ann. d'ocul. **118**:13, 1897.

3. Shoemaker, W. T.: Observations on Motais Operation for Ptosis, Ann. Ophth. **41**:608, 1907.

4. Taggart, H. J.: Modifications of Motais Operation, Tr. Ophth. Soc. U. Kingdom **53**:327-331, 1928.

5. Kirby, D. B.: A Modified Motais Operation for Blepharoptosis, Arch. Ophth. **57**:327-331 (July) 1928.

6. Morgan, O. G., cited by Greeves.[12]

7. Ellett, E. C., in discussion on Trainor,[13] p. 97.

8. Stephenson, cited by Grimsdale, H., and Brewerton, E.: Textbook of Ophthalmic Operations, Baltimore, William Wood & Company, 1937, pp. 34-51.

9. Duverger, C., and Velter, E.: Traité d'ophthalmologie, Paris, Masson & Cie, 1939, vol. 7, p. 456.

Because Parinaud,[2] and later Cannas,[10] sutured the tendon of the levator palpebrae muscle to the entire width of the superior rectus, no arch developed, and the curve of the upper lid was more normal in contour. However, the tendon of the levator palpebrae often pulled away from the superior rectus muscle, resulting in failure. To overcome this difficulty, Young[11] sutured the upper border of the tarsus to the superior rectus, whereas Greeves[12] fashioned two flaps, one from each side of the upper border of the tarsus, and sutured these flaps to the medial and lateral borders, respectively, of the superior rectus muscle. Trainor[13] prepared a single flap from the upper edge of the tarsus and, after passing it under the tendon of the superior rectus, sutured the free end of the tarsal flap to the main body of the tarsus. Jameson[14] incised the tarsus horizontally 2 or 3 mm. below its upper border, and through this incision he pulled the tendon of the superior rectus, thus tucking it on the anterior surface of the tarsus. In 1936, Dickey[15] placed a strip of fascia lata under the middle third of the superior rectus and sutured the two ends of the fascia lata to the anterior surface of the tarsus. Later, Gifford[16] passed the fascia lata under the entire tendon of the superior rectus. To avoid using foreign tissue in the operation, Wheeler[17] and Darier[18] fashioned flaps from the orbicularis muscle overlying the tarsus and then sutured these flaps to the superior rectus.

The advantages and disadvantages of utilizing the superior rectus muscle to support the lid have been cited before,[19] but they may bear

10. Cannas, cited by Wiener, M., and Alvis, B.: Surgery of the Eye, Philadelphia, W. B. Saunders Company, 1939, p. 331.

11. Young, G.: An Operation for Congenital Ptosis, Brit. J. Ophth. **8**:212, 1924.

12. Greeves, R. A.: Operation for Relief of Congenital Ptosis, Proc. Roy. Soc. Med. **26**:1478-1482 (Sept.) 1933.

13. Trainor, M. E.: Operation for Lid Ptosis, Tr. Sect. Ophth., A. M. A., 1935, pp. 93-97.

14. Jameson, P. C.: Surgical Management with Special Reference to Use of Superior Rectus Muscle, Arch. Ophth. **18**:547-557 (Oct.) 1937.

15. Dickey, C. A.: Superior Rectus Fascia Lata Sling in Correction, Am. J. Ophth. **19**:660-664 (Aug.) 1936.

16. Gifford, S. R.: Modification of Dickey Operation for Ptosis, Arch. Ophth. **28**:814-820 (Nov.) 1942.

17. Wheeler, J. M.: Correction of Ptosis by Attachment of Strips of Orbicularis Muscles to Superior Rectus Muscle, Tr. Sect. Ophth., A. M. A., 1938, pp. 130-137.

18. Darier, cited by de Blascovics, L.: Treatment of Ptosis: Formation of a Fold in the Eyelid and Resection of the Levator and Tarsus, Arch. Ophth. **1**:672-680 (June) 1929.

19. Berke, R. N.: Blepharoptosis, Arch. Ophth. **34**:434-450 (Nov.-Dec.) 1946.

repeating here. The main advantages may briefly be stated: 1. The upper lid moves synchronously with the globe in looking up and down. 2. A normal curve of the upper lid margin generally results from the Parinaud-Young-Trainer-Dickey type of procedure. 3. A natural-appearing fold is produced in the upper lid.

The chief disadvantages, briefly, are as follows: 1. Lagophthalmos is present during sleep, predisposing to keratitis as a result of exposure. 2. Normal winking and Bell's phenomenon are interfered with because the upper lid cannot move independently of the globe. 3. Hypotropia with diplopia occurs after operation. 4. An inverted V type of notch is often produced by the Motais-Shoemaker-Kirby type of operation because the adhesion between the superior rectus and the tarsus is too narrow.

The purpose of this article is to evaluate this type of operation for correction of ptosis by determining in what percentage of cases the aforementioned advantages and disadvantages are associated with the operation.

RESULTS OF THIRTY-FIVE MOTAIS-PARINAUD OPERATIONS

During the fifteen years at the Institute of Ophthalmology of the Presbyterian Hospital prior to this report 114 operations for ptosis have been performed in which the lifting power of the superior rectus muscle was utilized. The operations represented 39 private and 54 clinic patients. Letters were sent by the social service department to all 54 clinic patients asking them to report to the clinic for a final postoperative examination. Twenty-three patients responded and were personally examined; 4 others had adequate and reliable notes on their charts. After the private patients as a group and all the clinic patients with inadequate records were eliminated, a series of 35 operations on 27 clinic patients (8 had bilateral ptosis) were available for study.

In all cases a history was taken to determine whether the ptosis was congenital or acquired. Vision was determined when possible, and when this was impossible, as with young children, note was made of which eye was preferred for fixation. The width, and sometimes the length, of the palpebral fissures was noted with and without the assistance of the frontalis muscles, to determine what degree of function of the levator palpebrae was present, if any. Attention was paid to the function of the extraocular muscles, especially the superior rectus muscles. Any abnormal findings were also noted. In many cases children were given gum to chew to bring out the Marcus Gunn jaw-winking phenomenon, if present. As a general rule, all patients with some function of the levator palpebrae were sent to the hospital for resection of this muscle. In a few cases, in which this procedure was

unsuccessful, some modification of the Motais operation was performed as a second procedure.[20] Any weakness of the superior rectus was taken as a contraindication to the Motais type of operation, but in a few of the cases in which resection of the levator muscle had been a failure the Motais type of operation was performed, even though the superior rectus muscle was weak.

Of the 35 cases in which the operation was performed, the superior rectus was considered normal [21] in 32, weak in 2 and overactive in 1.[22]

Clinically the cases could be divided into four groups: Group 1 comprised 26 cases with normal superior rectus muscles; group 2, 2 cases with a weak homolateral superior rectus muscle; group 3, 3 cases of the Marcus Gunn jaw-winking phenomenon, and group 4, 4 cases of blepharophimosis. This classification was followed because it was thought that the results of the operation might be influenced by the type of ptosis present.

GROUP 1.—On the 26 eyes the following operations were carried out, with the results noted:

1. On only 14 of the 50 cases in which the Kirby-Motais operation was performed did the patient return for a final postoperative study. Of these 14 cases, there was some improvement of the ptosis in 10 and no improvement in 4. Of the 10 cases in which the ptosis was improved, postoperative weakness of the homolateral superior rectus was present in 7; no such weakness was discernible after operation in 3, and an inverted V notch of the margin of the upper lid developed in 5.[23]

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20. If these two procedures were unsuccessful, some type of operation on the frontalis muscle (usually the Reese) was done.

21. In young children it was often difficult in the presence of complete ptosis to be certain that the homolateral superior rectus was normal; therefore, in a few cases in which the superior rectus muscle was weak it may have been classified as normal.

22. No cause for the overaction of the superior rectus was noted in this case. Overaction of the superior rectus on the side of the ptosis must be considered rare, for this case was the only one found in a series of 200 cases of congenital ptosis recently studied.

23. In many cases of postoperative notch formation, the nasal half of the lid was usually well elevated to uncover the pupil, but the lateral half sagged, so that when the patient looked to the side of the ptosis the cornea became covered by the sagging upper lid. In these cases it was difficult for the examiner manually to elevate the patient's upper lid (in order) to uncover the pupil and so enable the patient to fix with his eye so that the action of the superior rectus could be studied. In one respect, this sagging of the upper lid proved to be a blessing in disguise, because when weakness of the superior rectus had been produced by the operation, diplopia was absent, owing to the fact that the upper lid covered the pupil in the field of action of the weak superior rectus muscle.

2. In 2 cases the eye was subjected to the classic Motais procedure. In both cases the ptosis was improved, but in 1 case a notch deformity developed. In both cases some weakness of the homolateral superior rectus developed after operation.

3. In 1 case the Shoemaker-Motais technic was employed, with postoperative weakness of the superior rectus, improvement of the ptosis and notch formation.

4. In 6 of the 16 cases in which the Parinaud-Young technic was employed the patient returned for study. Of these 6 cases, improvement in the ptosis occurred in 5 and none in 1. In 3 of the 6 cases discernible weakness of the homolateral superior rectus developed, and in 3 it did not.[24]

5. In only 2 of the 10 cases in which the Wheeler orbicularis muscle transplantation for ptosis had been done did the patient report for final postoperative study. Improvement of the ptosis was apparent in 1 of the cases and none in the other. The patient with improvement showed weakness of the superior rectus but no notch formation in the upper lid.

6. In only 1 of the 17 cases in which the Dickey operation was performed did the patient return for study. In this case there was no improvement in the ptosis, no arch formation and no induced weakness of the superior rectus.

Of the 26 cases in group 1, in which the superior rectus muscle was normal, improvement followed the procedure used in 19 (73 per cent) and in 7 ptosis did not improve. Of the 19 cases in which improvement occurred, postoperative weakness of the homolateral superior rectus muscle followed in 14 (74 per cent) and did not in 5. In 7 (54 per cent) of the 13 cases showing improvement with the Motais-Kirby-Shoemaker operation a notch deformity developed in the upper lid, while in none of the 6 eyes showing improvement with the Parinaud-Young-Wheeler-Dickey operation did such a deformity develop.

From the foregoing figures, it would seem that in about three quarters of all cases in which the superior rectus muscle was normal and the Motais-Parinaud principle was observed, the ptosis improved but that in about the same percentage of these cases in which the ptosis improved weakness of the superior rectus muscle developed after the operation. In about one-half the cases in which the ptosis improved with the Motais technic, in which a narrow adhesion is produced between

24. It should be noted that in none of the cases in which the Parinaud-Young operation was performed did the Gothic type of arch defect of the upper lid develop. The absence of the notch formation was attributed to the width of the attachment between the superior rectus and the tarsus, in contrast to the narrowness of this band in the Motais operation.

the superior rectus and the tarsus, a notch deformity of the upper lid developed, whereas in none of the cases in which operation was carried out by the Parinaud method, in which a wide adhesion is produced, did such a deformity develop.

GROUP 2.—Eleven cases of the entire group belonged to group 2; i.e., in each case in this group weakness of the superior rectus alone or of the superior rectus and the inferior oblique occurred on the same side as the ptosis. In only 2 of these 11 cases did the patients return for study. In 1 of these 2 cases the classic Motais operation was performed, with fair improvement of the ptosis but with notch formation. The weakness of the superior rectus persisted after operation. In the other case a Dickey operation was performed, with good improvement of the ptosis and no notch formation, but with residual postoperative weakness of the superior rectus muscle. The end result in these 2 cases with weak superior rectus muscles tends to show that the ptosis can be improved even though the superior rectus is weak, but that the weakness of the superior rectus muscle persists or is accentuated by the operation. These 2 cases also confirm the experience derived from group 1, namely, that in most cases a notch deformity of the upper lid develops with any of the Motais technics, whereas in cases in which the Parinaud technic is used such a deformity does not develop.

GROUP 3.—In only 8 cases in the entire group studied was the jaw-winking phenomenon of Marcus Gunn exhibited. Of the 8 patients, 3 returned for study, 2 of whom had had a Parinaud-Young operation. In both, several millimeters of the entire width of the tendon of the levator orbicularis had been excised under the skin to correct the phenomenon, with production of complete ptosis. Each patient had a normal superior rectus muscle before operation but exhibited definite weakness of this muscle after operation. One patient had what was considered a good, and the other a fair, result. Neither patient had a notch deformity.

On the third patient of this group with the jaw-winking phenomenon a Wheeler orbicularis muscle transplantation for ptosis was performed. This patient had a normal superior rectus before operation but manifested weakness of this muscle after operation without notch formation. In all but 1 of the 3 patients the jaw-winking phenomenon was completely cured; in the exception slight elevation of the lateral half of the upper lid was shown with exaggerated movements of the jaw to the opposite side, but only when the patient was looking down. I believe that the treatment used for these 3 patients is the method of choice for correction of ptosis associated with the jaw-winking phenomenon. First, the latter abnormality must be cured by tenotomizing or tenectomizing the aponeurosis of the levator muscle, thus converting an incomplete

ptosis into a complete one. Then, the ptosis should be corrected by utilizing the lifting power of the superior rectus, preferably by one of the technics which produce wide adhesions between the superior rectus and the tarsus or, if one prefers, by utilizing the lifting power of the frontalis muscle.

GROUP 4.—There were 4 cases of ptosis associated with blepharophimosis. In some of these cases the palpebral fissures were narrow, S-shaped slits 1 or 2 mm. wide and only 15 mm. long. The width between the inner canthi over the bridge of the nose sometimes measured as much as 40 mm.[25]

In 4 cases of ptosis associated with blepharophimosis in this group, the Kirby-Motasis operation was performed. In 4 cases there were normal superior rectus muscles before operation with fair improvement in the ptosis in 2 cases and no improvement in the other. In 2 cases with improvement a notch developed in the upper lid.

Patients with ptosis and blepharophimosis present one of the most difficult problems in ptosis surgery, because not only must the ptosis be corrected but inner canthi must be approximated and the palpebral fissures lengthened. Dimmetry [26] called attention to the fact that in these cases the phimosis must first be corrected. It should be added that the great distance between the inner canthi must be shortened also before correction of the ptosis is attempted. Lengthening the fissures by means of an external canthoplasty is a simple procedure. At the same time, the external canthal ligaments may be severed, so that the palpebral fissures can be pulled nasally. The inner canthi can be pulled closer together by shortening or transplanting the internal canthal ligaments or by excising a piece of skin over the bridge of the nose, according to any of the various methods designed to cure epicanthus. In our experience, none of these methods is eminently successful in shortening the distance between the inner canthi, although we have not used tantalum wire for this purpose. When the fissures have been lengthened and the deformity of the inner canthi has been corrected, the ptosis can be corrected.

COMMENT

The success of any operation for ptosis must depend not only on the operation selected but also on the nature or type of ptosis present. Therefore, in an attempt to evaluate the results for the superior rectus type of operation for ptosis, the series of 35 cases included in this

25. In young normal children the length of each fissure measures from 25 to 28 mm., and the distance between the inner canthi averages 25 to 30 mm. In most cases in group 4 the eyeballs were normally placed, but the pupils were sometimes partly covered by the displaced inner canthi, especially in adduction.

26. Dimmetry, T. J.: Hereditary Ptosis, Am. J. Ophth. **4**:655-658, 1921.

survey were divided into four clinical groups, with the hope that such classification would help in explaining the failures. Group 1 comprised 26 cases of ptosis with normal superior rectus muscles, in which five surgical technics were used; group 2, 2 cases of ptosis with weak superior rectus muscles in which two surgical technics were used; group 3, 3 cases of ptosis complicated by the jaw-winking phenomenon of Marcus Gunn, in which two surgical technics were used, and group 4, 4 cases of ptosis complicated by blepharophimosis, in all 4 of which the same technic was employed.

When the 35 cases are considered as a group, without regard to this classification or to the operation performed, the superior rectus muscle was normal before operation in 32, weak in 2 and, overactive in 1. After operation weakness of the superior rectus developed in 24 cases, including the case with overaction of this muscle before operation and the 2 cases with preoperative weakness of the superior rectus muscle. This postoperative weakness usually appeared only in the cases in which the ptosis was improved as a result of the operation (26 cases), but it developed also in 6 of the 9 cases in which no improvement was shown. In not all the cases in which the ptosis improved did weakness of the superior rectus muscle develop after operation, for in 8 of the 26 cases of improvement the superior rectus appeared normal clinically. These cases in which the superior rectus muscles were apparently normal after operation were generally those of bilateral ptosis in which the sagging of the lateral half of the upper lid of the eye operated on covered the pupil of this eye in abduction, so that the opposite eye took up fixation in this position, thus covering any induced weakness of the superior rectus muscle operated on. It is remarkable that only 2 patients complained of persistent diplopia. The rest either had amblyopia ex anopsia before operation or learned suppression later.

As might be expected, only in those cases in which the Motais-Shoemaker-Kirby technic had been carried out did a notch in the upper lid develop, presumably because of the narrow attachment between the superior rectus and the upper lid, whereas in none of the cases in which wide adhesions were produced between the globe and the upper lid did such a deformity develop.

In 26 of the 35 cases the ptosis was improved by operation; in 4 cases the correction of the ptosis was excellent; in 14 cases the improvement was considered good, and in 8 cases there was only fair improvement. In 9 cases in which little or no improvement followed the operation the adhesion between the upper lid and the superior rectus had pulled away. In 7 of these 9 cases of failure the superior rectus muscles were normal (group 1) and in 2 failure followed the Kirby-Motais operation in patients with blepharophimosis (group 5).

SUMMARY AND CONCLUSION

A survey of 35 cases of operation for ptosis in which the lifting power of the superior rectus was utilized showed that in about 11.4 per cent of the cases the ptosis was excellently corrected, that in 40 per cent improvement was good, that in about 23 per cent improvement was slight and that in the rest (25.6 per cent) there was no improvement. Six different technics were used, as follows: In 18 cases the Kirby-Motais technic was employed, with improvement in 12 cases; in 3 cases, the Motais operation, with no failures; in 1 case, the Shoemaker operation, with improvement; in 8 cases, the Parinaud-Young operation, with failure in 1 case; in 3 cases the Wheeler orbicularis muscle transplantation, with improvement in 2 cases, and in 1 case, the Dickey operation, with failure. An attempt was made to trace the failures to the type of ptosis present by dividing the cases into four groups: Group 1 was made up of 26 cases of ptosis with normal superior rectus muscles, group 2, of 2 cases with weakness of the superior rectus muscles; group 3, of 3 cases of the jaw-winking phenomenon of Marcus Gunn, and group 4, of 4 cases of ptosis with blepharophimosis. Because the number of cases in groups 2, 3 and 4 were too few to permit one to make comparisons, this classification did not help in explaining the failures.

Considering the series of 35 operations as a whole, one may say that in about 73 per cent of cases some improvement was derived from the operation for ptosis, but at the expense of postoperative weakness of the superior rectus in about 70 per cent of the cases in which such improvement was obtained. The Motais, the Kirby and the Shoemaker technic utilized a narrow band of tissue from the superior rectus to the upper tarsus, resulting in a notch of the upper lid in 73 per cent of the cases of successful correction. In the Parinaud, the Young, the Wheeler and the Dickey operation, in which wide adhesions were formed between the upper tarsus and the superior rectus muscle, no such notch developed. It is interesting to note that in not a single case of the entire series did any complaint or evidence of ulceration of the cornea occur, over periods of three to ten years after the operation.

The results in the series of 35 cases of congenital ptosis may be summarized as follows:

1. Utilization of the superior rectus muscle to correct ptosis in 35 cases of congenital ptosis gave an excellent result in 4 cases (11.3 per cent), a good result in 14 cases (40 per cent), a fair result in 8 cases (22.8 per cent) and no improvement in 9 cases (25.9 per cent).

2. In about 72 per cent of the cases (16 of 22 cases) in which the Motais-Shoemaker-Kirby technic was used, improvement followed the operation, whereas in 76.9 per cent (10 of 13 cases) in which the

Parinaud-Young-Dickey procedure was employed, the ptosis was benefited.

3. Utilization of the superior rectus to correct ptosis induced weakness of the superior rectus muscle in 74.3 per cent of the cases (26 of 35 cases).

4. In exactly 62.5 per cent of the cases (10 of 16 cases) in which improvement followed the Motais-Shoemaker-Kirby technic, in which a narrow adhesion is produced between the upper lid and the globe, a notch deformity resulted in the upper lid, whereas in none of the cases in which the Parinaud-Young-Dickey procedure was used did such deformity develop.

5. The upper lid moved nicely up and down with the movements of the globe in the cases of successful correction, and a natural-appearing upper lid fold generally resulted.

6. Lagophthalmos in sleep was present in most of the cases of corrected ptosis, but no evidence of corneal ulceration occurred.

7. In most cases normal winking and the Bell phenomenon were interfered with.

8. An attempt to evaluate the superior rectus type of operation on the basis of the division of cases of congenital ptosis into four groups resulted in failure because the cases in each group were too few to justify conclusions.

This type of procedure should be reserved only for cases of complete ptosis in which the levator palpebrae muscle is completely paralyzed and the superior rectus muscle is active.

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PROGRESSIVE MUSCULAR DYSTROPHY INVOLVING THE EXTRAOCULAR MUSCLES

Report of a Case

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THE DIAGNOSIS of palsy of an extraocular muscle usually signifies to the ophthalmologist a lesion of its nerve supply. For example, a paralysis of the external rectus muscle is accepted as indicating a lesion of the sixth nerve or of its nucleus. This is so common that there is a great tendency to forget the rarer occurrence of a primary muscular disorder as a cause of impairment. Many such errors appear in the literature; a critical review of the published reports since 1890 indicated that in some of the cases of ophthalmoplegia the paralysis was due not to the nerve lesions to which it was ascribed, but probably to myasthenia gravis or one of the types of muscular dystrophy.

In 1890 Fuchs [1] reported 5 isolated cases of bilateral ptosis in female patients. In 3 of these cases the ptosis developed late in life; in the other 2 it either was congenital or began in early infancy. In 1 of these cases a portion of the levator muscle was removed, and Fuchs reported that the muscle fibers had undergone what was thought to be extensive degeneration, with increase in connective tissue but with no fatty change. This histologic study of an extraocular muscle in a case of palsy is unique among the early investigators.

Clinical reports by Beaumont,[2] Wilbrand and Saenger,[3] Collins,[4] Altland,[5] Cooper,[6] McMullen,[7] Bradburne,[8] Crigler,[9] McMullen and

This work was done under the William L. Hernstadt Fund at the Montefiore Hospital.

1. Fuchs, E.: Arch. f. Ophth. **36**:234, 1890.
2. Beaumont, W. M.: Tr. Ophth. Soc. U. Kingdom **20**:258, 1900.
3. Wilbrand, H., and Saenger, A.: Neurologie des Auges: Die Pathologic der Bahnen und Centren der Augenmuskeln, Munich, J. F. Bergmann, 1921, vol. 8, p. 121.
4. Collins, E. T.: Tr. Ophth. Soc. U. Kingdom **29**:225, 1909.
5. Altland, W.: Arch. Ophth. **38**:296, 1909.
6. Cooper, H.: Brit. M. J. **1**:917, 1910.
7. McMullen, W. H.: Tr. Ophth. Soc. U. Kingdom **32**:111, 1912.
8. Bradburne, A. E.: Tr. Ophth. Soc. U. Kingdom **32**:142, 1912.
9. Crigler, L. W.: Arch. Ophth. **43**:268, 1914.

Hine [10] and Nikitin,[11] from 1900 to 1929, include isolated cases of ophthalmoplegia and others with a hereditary background. Cases of congenital ophthalmoplegia also were reported. These authors suggested various possibilities for the etiologic factor, from atrophy or nondevelopment of the oculomotor nuclei to arrested muscular development. In none of these reports were there histologic studies of the extraocular muscles.

In 1939 Elliot [12] presented a case report entitled "Myopathic Wasting Associated with Ptosis and External Ophthalmoplegia." This report, unfortunately unsupported by biopsy, is the earliest in the literature of clinical progressive muscular dystrophy involving the extraocular muscles. Martin,[13] commenting on Elliot's report, stated that, although the condition described would usually be considered progressive nuclear ophthalmoplegia, a good case could, in his opinion, be made out for primarily a myopathic rather than a nervous origin.

Sandifer [14] in 1946 presented the first detailed histologic study of an extraocular muscle with myopathic degeneration in a case of chronic progressive ophthalmoplegia. Sandifer's patient, aged 29, had symmetric and progressive drooping of the eyelids, which began before the age of 20. From the age of 20 his eyeballs had become increasingly immobile. His parents were unrelated, and there was no family history of ptosis or of muscular weakness. There was no defect of any of the body muscles except in the ocular group. The eyeballs were almost fixed in position, with hardly any mobility. Both orbicularis oculi muscles were weak. There was no internal ophthalmoplegia. The absence of any response to the intramuscular injection of neostigmine methylsulfate ruled out myasthenia gravis. Sensory tests showed no abnormalities. The electrocardiogram suggested branch bundle block. Biopsy of a portion of the external rectus muscle indicated myopathic degeneration rather than neuropathic atrophy. Degeneration and disintegration of individual fibers were noted. There were extremely few of the very thin fibers seen with atrophy.

REPORT OF CASE

H. F., a white man aged 26, was admitted to Montefiore Hospital on July 16, 1947. He was one of a sibship of 6, the other 5 being in good health and without any muscular defects. The patient's mother was born in Russia and his father in Argentina, and there was no consanguinity. There was no history of any muscular disorder in the family except that his mother had a right esotropia. This was concomitant and nonparalytic, had been present since early childhood and was not progressive. According to the history obtained, his maternal and paternal grandparents had no muscular disorders.

10. McMullen, W. H., and Hine, M. L.: Brit. J. Ophth. **5**:337, 1921.
11. Nikitin, M. P.: Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:575, 1929.
12. Elliot, F. A.: Proc. Roy. Soc. Med. **32**:876, 1939.
13. Martin, J. P., in discussion on Elliot.[12]
14. Sandifer, P. H.: J. Neurol., Neurosurg. & Psychiat. **9**:81, 1946.

His mother said that the patient's birth, as well as the pregnancy, had been normal but that he seemed weak from the time of his birth. He sat up at 6 or 7 months of age and walked at 18 months. He fell often in early life. He

Fig. 1.—Patient with progressive muscular dystrophy. The ptosis and divergent strabismus, as well as the general deficiency of the musculature, are noteworthy.

Fig. 2.—Eyes in the primary position. There is an alternating divergent strabismus. The ptosis is not shown, as the lids were elevated by the frontalis muscle for this photograph.

started to speak later than his brothers and sisters and always had a speech difficulty. He went to school in Cuba from the ages of 8 to 14 years and was at least as capable as his classmates. The patient stated that during the six

years since the age of 20, his general weakness had increased. About six years prior to his admission ptosis developed and became conspicuous, and the right eye began to diverge. During the preceding two years he had lost about 30 pounds (13.6 Kg.) in weight and much of his strength. He had occasional difficulty in swallowing.

General Physical Examination.—The patient was 5 feet 7½ inches (171.5 cm.) in height and weighed 86 pounds (39 Kg.). He was extremely emaciated, with generalized and symmetric wasting of all muscle groups. All the muscles were weak, and no group was notably weaker than the others. There were no fibrillations and no sensory changes. The deep and superficial reflexes were within normal limits. The lower jaw was prominent, so that the facies was prognathic. He spoke with difficulty, forcing out the words, which frequently

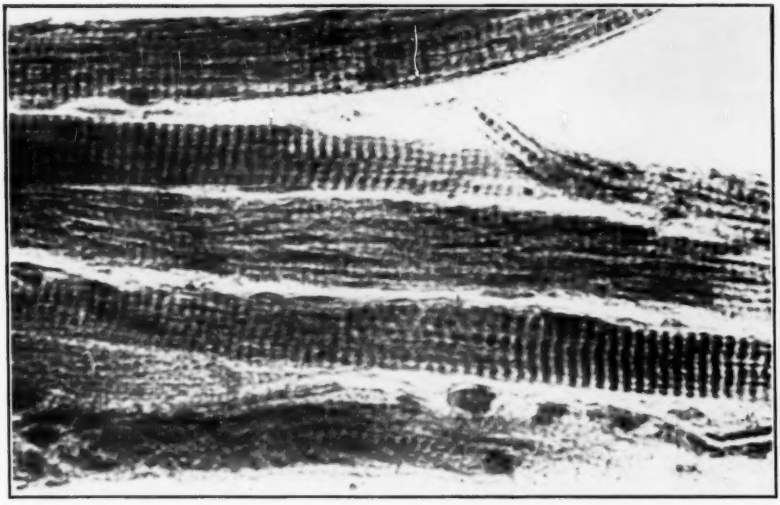

Fig. 3.—Section from a normal internal rectus muscle. Note the regularity of the fibers and the cross striations.

were mere whispers. He had considerable lordosis and walked with a wide-based gait, lifting his feet high and swaying from side to side with each step. There was bilateral equinovarus. The blood pressure was 118 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. The urea nitrogen of the blood was 13.4 mg. and the blood sugar 81 mg. per hundred cubic centimeters. The urine was normal. The blood count revealed 13.5 Gm. hemoglobin, 4,340,000 red blood cells and 9,350 white blood cells per cubic millimeter, with a normal differential count. Roentgenographic examination of the heart, lungs, diaphragm, mediastinum and thoracic cage revealed no abnormalities. Posteroanterior and right lateral stereoscopic roentgenograms of the skull were normal. The heart sounds were normal. The electrocardiogram revealed a right axis deviation with large R waves in leads CF_1 and CF_3, indicating probable myocardial hypertrophy of the right side of the heart. Injection of 1.5 mg. of neostigmine methyl-

sulfate resulted in no recovery of muscle power. Other findings in the physical examination were noncontributory.

Ophthalmologic Examination.—Visual acuity was 5/100 in each eye, and a correction of —9 D. sphere for each eye gave 15/50. With the eyes in the primary position, there was an alternating exotropia of 27 △ for distance and of 47 △ for near vision. The patient fixated with either eye, depending on the field of gaze. There was considerable ptosis of both upper lids, so that

Fig. 4.—Section of the internal rectus muscle from the case of progressive muscular dystrophy. Note the irregularity of the fibers, with faint cross striations visible in a few fibers, whereas others show pronounced swelling and loss of cross striations. The magnification is same as that for figure 3.

the lids covered the upper one-half of each cornea, serving as a pinhole for the pupil and causing slight visual improvement for the patient, who had worn no glasses up to the time of this hospitalization. Ocular movements were extremely limited, owing to generalized paresis of all the extraocular muscles, of varying amount, but most pronounced in the internal rectus muscles. He had only 5 D. of accommodation in each eye, whereas the normal amount for a subject 26

years of age is 8 D., a deficiency suggesting involvement of the ciliary muscles in the myopathic process. The pupillary reactions were prompt to light and in the accommodation and convergence responses. The media were clear, and no opacities were noted in the lens on examination with the slit lamp. Examination of the fundus revealed an inferior conus at the disks in each eye.

A resection of the left internal rectus was performed on July 31, 1947 for improvement of the squint. At that time some of the internal rectus muscle was obtained for histologic study. Two pieces of muscle tissue were removed, one near the tendious insertion of the muscle on the globe and another farther back in the belly of the muscle.

Histologic Examination.—The excised muscle showed extensive changes. Most of the myofibrils were swollen and degenerated, with some replacement by fibrous tissue and loss of their cross striations. There was an increase in the number of sarcolemmal nuclei. A small number of myofibrils had some resemblance to the normal; but even these took the stain poorly; their outlines were a bit irregular, and their cross striations were faint. A few myofibrils were vacuolated, as in lipid degeneration. This confirmed the diagnosis of muscular dystrophy.

COMMENT

The case reported here is the second of progressive muscular dystrophy of the extraocular muscles proved by histologic study of the involved muscle. In the first case, reported by Sandifer [14] in 1946, the dystrophy appeared to be limited to the extraocular muscles. In our case, the muscular wasting was extensive and symmetric over the entire body, and the extraocular muscles were involved as part of a general muscular dystrophy. The striking fact presented by Sandifer's case is the occurrence of the myopathy in the extraocular muscles alone, at least apparently, in its clinical manifestations. Consequently, in cases of ophthalmoplegia, one of the diagnoses to be considered is progressive muscular dystrophy. A microscopic study of paretic muscles in a larger number of cases would be of interest.

The literature is confusing in explanation of the various types of palsy. The features of progressive muscular dystrophy include swelling of some of the muscle fibers with change in the staining property of the sarcoplasm, true fatty degeneration and replacement of muscle fibers with fibrosis, with some normal, or more or less normal, myofibers in proximity. In progressive muscular dystrophy there is a true dystrophic change in the individual myofiber. This change is primary in the myofiber, with no known change in the nerve supply.

Simple atrophy of muscle is due to a defect in the nerve supply of the muscle. The defect may be in the nucleus or anywhere along the nerve. The atrophy is the result of paralysis of the muscle, followed by wasting from disuse and possibly trophic changes. The fibers shrink, but they retain the essential character of the muscle, with presentation of the cross striations. Such palsy is common in the eye and may affect any of its muscles, producing a paralytic squint. The ocular

muscles have not been studied to any extent in such cases, but the body musculature has been extensively studied in cases of similar palsies which followed disease or injury to the nervous system, such as poliomyelitis and amyotrophic lateral sclerosis. Myasthenia gravis may cause similar muscular atrophy. Multiple sclerosis may cause extraocular palsies with atrophy of the muscle involved. It is usually possible to differentiate between primary muscular dystrophy and muscular atrophy by the history, by physical examination and, even more surely, by biopsy of the muscle.

An interesting feature of our case is the probable involvement of the myocardium, as demonstrated by the electrocardiographic changes. Defects of heart muscle have rarely been reported in cases of progressive muscular dystrophy, but they may well be less rare than is supposed. The extraocular muscles in cases of generalized primary dystrophy may also be affected more frequently than is supposed. The dystrophic changes in the myofibers may cause only subclinical palsies, which should be looked for. Careful histologic study of extraocular muscles in cases of primary muscular dystrophy, even without clinical evidence of extraocular muscular palsies, would be of great interest.

No hereditary factor could be elicited in our case. This does not rule out the possibility that the disease may be inherited as a recessive or as a sex-linked recessive factor. If heredity is a factor, the mode of inheritance remains to be determined by further investigation.

SUMMARY

Progressive muscular dystrophy was the cause of ptosis and divergent squint in the case presented. This was proved by histologic study of a section from the internal rectus muscle.

This case is the second in which histologic study of the extraocular muscles has been reported and the first in which involvement of the extraocular muscles has been demonstrated in a case of generalized progressive muscular dystrophy.

The differentiation of primary muscular dystrophy and secondary muscular atrophy is discussed.

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TRAUMATIC CHOROIDITIS

Review of Literature and Report of Ten Cases

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THE TERM "rupture of the choroid," as it is ordinarily used, does not refer to a single, well defined disease entity but, rather, is made to apply to two heterogeneous morbid states with dissimilar etiology, pathology and prognosis: disruption of the choroid due to direct injury and that due to indirect injury. These two choroidal changes can even be distinguished according to the region in which they occur. In the case of direct injury, the trauma results at the place of impact, and the rupture usually reaches so far in the anterior direction that its frontal end extends beyond the field of ophthalmoscopic examination. In the case of indirect injury, on the other hand, the trauma is produced by contrecoup, and the choroidal changes appear invariably in the posterior segment, distal to the area exposed to the impact. The present discussion is restricted to the latter, and more frequent, type of injury to the choroid.

The earliest report of rupture of the choroid encountered is a description of 2 cases of indirect injury published by von Graefe,[1] in 1854. In the first of these cases a narrow, reddish brown line, shaped like a crescent, with its convexity in the anterosuperior direction, was present close to the optic disk and was diagnosed as a residuum of choroidal hemorrhage. Several months later, after disappearance of ecchymosis, a deposit of light brown pigment persisted, as well as a number of white streaks, representing breaks in the continuity of the choroid.

The characteristic appearance of the vascular coat following rupture due to indirect injury has been described by a number of authors.[2] A single break may have occurred, or multiple tears of various sizes, sometimes as many as six, may be encountered. Godfredsen [3] noted

1. von Graefe, A.: Two Cases of Rupture of the Choroid, Arch. f. Ophth. **1**:402-403, 1854.

2. *(a)* Haab, O.: Atlas of Ophthalmoscopy, ed. 2, Philadelphia, W. B. Saunders Company, 1909, p. 80. *(b)* Oatman, E. L.: Diagnostics of the Fundus Oculi, Troy, N. Y., The Southworth Co., 1920, p. 59. *(c)* Parsons, J. H.: Diseases of the Eye, ed. 7, New York, The Macmillan Company, 1934, p. 422.

3. Godfredsen, E.: Re-Examination of Central Ruptures of the Choroid, Acta ophth. **20**:337-350, 1942.

single tears in two thirds of all instances, while dual lesions appeared in 25 per cent of choroidal ruptures.

The fissures are usually localized in an area close to the optic papilla; in their most characteristic form they follow the outline of the disk in a concentric pattern or extend parallel with the equator. Multiple lesions are usually concentric. The linear lacerations generally involve the macular region; but in a case reported by Oatman [2b] there appeared two concentric lesions, entirely limited to the nasal portion of the fundus. In shape, the typical choroidal rupture can be compared to segments of a circle, or to circular arches, wider at the center, narrowing down toward each extremity and often ending in forklike branches. But irregular shapes are by no means uncommon, and the patterns are sometimes so complicated as to defy verbal description.[4] Pigmentation is usually present, and the retinal vessels traverse the gaps in the choroid uninterruptedly.

Various irregular patterns have been reported in the literature. Goar [5] encountered a rupture of the choroid in the shape of an inverted Y, associated with angioid streaks. Choroidal rupture, concomitant with a cyst of the vitreous, which later ruptured, was described by Rosen.[6] In the macular region, a pronounced choroidal tear extended vertically for a distance of about 3 disk diameters; over the center of this rupture a peculiar biconvex band was seen, which frayed out at each end, in semicircular astral radiations. According to Kaminskaya,[7] choroidal ruptures due to battle injury differ in appearance from those following accidents in civilian life. Such traumatic lacerations may be encountered in any part of the fundus, and they assume the pattern of intertwining broken zigzag lines.

It has been estimated that rupture of the choroid occurs at a rate of about 1 per thousand patients with ophthalmic disorders.[8] Godfredsen,[8] however, arrived at a figure of only 0.2 per thousand. In a series of 300 cases of ocular war lesions, Bellows [9] encountered 27

4. Bedell, A. J.: Traumatic Changes in the Retina, Choroid, Nerve Head and Vitreous, Tr. Sect. Ophth., A. M. A., 1941, pp. 25-39; J. A. M. A. **117**:1774-1778 (Nov. 22) 1941.

5. Goar, E. L.: Angioid Streaks in the Ocular Fundus with Traumatic Rupture of the Choroid, Am. J. Ophth. **21**:907-910 (Aug.) 1938.

6. Rosen, E.: Rupture of the Choroid Associated with Cyst of Vitreous, Brit. J. Ophth. **29**:486-489 (Sept.) 1945.

7. Kaminskaya, Z. A.: Clinical Symptoms and Therapy of Indirect Ocular Injuries, Vestnik oftal. (pt. 2) **22**:7, 1943; abstracted, Am. J. Ophth. **27**:324-325 (March) 1944.

8. Roemer, P.: Textbook of Ophthalmology, New York, Rebman Co., 1917, p. 337.

9. Bellows, J. G.: Observations on Three Hundred Consecutive Cases of Ocular War Injuries, Am. J. Ophth. **30**:309-323 (March) 1947.

instances of nonpenetrating or contusion injuries, and among them only 1 case of so-called rupture of the choroid. According to Siegrist,[10] the amount of functional impairment depends mainly on the degree to which the trauma has involved the center of the choroid.

ETIOLOGY

Any theory based on the assumption that an actual break occurs within the choroid, and that the lesion results directly from contrecoup, will have to account for a consistent, peculiar finding, namely, that a blow inflicted on the anterior segment of the eye may lead to trauma distal to the point of impact in only one of the three tunics of the fundus, even though the choroid, situated between the retina and the sclera, is in close contact with these other structures. It is, therefore, hardly surprising that the causation of choroidal rupture is a highly controversial subject.

Siegrist,[10] in 1895, observed 4 cases in which the eyeball had been injured by blunt violence without, however, causing perforation. As five years earlier Wagenmann[11] had experimentally produced similar choroidal lesions in rabbits by cutting one or more of the short posterior ciliary arteries, Siegrist was inclined to assume accidental severing of these vessels as the cause of indirect rupture of the choroid in man. He was unable, however, to exclude a number of other possible ways in which so-called acute traumatic chorioretinitis might have been produced, i. e., by subchoroidal hemorrhage, thrombosis or contusion of the ciliary vessels, resulting in bleeding through diapedesis.

In 1917, Roemer[8] reviewed five etiologic theories prevalent at that time. Von Arlt suggested that the impact leads to flattening of the anterior structures of the globe, with dilatation of the equator and distention of the choroid. Another explanation, which Roemer attributed to Becker, was to the effect that pressure of the posterior segment against the optic nerve produces invagination of the nerve, causing choroidal rupture. A similar theory was advanced by Highes, who assumed that the fundus of the eye was stretched by the optic nerve, with subsequent laceration of the choroid. Lohman maintained that the rupture occurred at the point where the direction of pressure was reversed. According to Stoewer, trauma to the vascular coat was due to the difference in elasticity between sclera and choroid; Roemer himself was in agreement with the latter explanation.

10. Siegrist, A.: Traumatische Ruptur von Ciliararterien, Mitt. a. d. klin. u. med. Inst. d. Schweiz. **9**:554, 1895; cited by Osterberg.[18]

11. Wagenmann, A.: Experimentelle Untersuchungen über den Einfluss der Circulation in der Netzhaut- und Aderhautgefässen auf die Ernährung des Auges, insbesondere der Retina, und über die Folgen der Sehnervendurchschneidung, Arch. f. Ophth. **36**:1-120 (Dec.) 1890.

Oatman [2b] arranged the existing etiologic theories under four heads: (1) causation through contrecoup; (2) compression of the eyeball against the optic nerve; (3) sudden arrest of rotation of the globe, caused by the optic nerve, and (4) sudden arrest caused by the short posterior ciliary arteries. Oatman remarked that the number of differing theories advanced was a measure of their inadequacy. He suggested that the crucial point of any etiologic theory must be an explanation of the observation that ruptures of the choroid always occur at the posterior pole, usually on the temporal side, and concentric with the papilla. Oatman's own theory proceeded from the observation that the usual location of choroidal ruptures corresponds to the point of attachment of the oblique muscles. He assumed that when sclera and choroid recede under the impact of concussion, spasmodic contraction of the oblique muscles will take place, and that the choroid is broken across the rigid edge formed by the muscle fibers. The retina escapes laceration, as it is not attached to the oblique muscles.

Kaminskaya [7] advanced an interesting explanation based on observations in a field hospital. According to his theory, concussion of the eyeball often produces subluxation of the lens. The disturbance sets up a reverse wave in the posterior segment, separating the vitreous from the retina and creating a vacuum. The concussion simultaneously affects the vascular walls themselves, giving rise to spasm, increased permeability and secondary dilatation. These two results of concussion, vacuum and vascular disturbance, combine to produce hemorrhage and choroidal changes.

Hudelo, Guillaumat and Maussion,[12] in reporting 4 cases, suggested that choroidal lesions of this type are produced through traumatic necrosis. Gangrene develops at the precise point at which the shock waves, proceeding in opposite directions through the walls of the globe, come into a violent conflict. The shape of the choroidal lesion depends on the course of the shock waves, and the typical arciform appearance results from passage along the meridian.

The hypothesis of Hudelo, Guillaumat and Maussion, that so-called rupture of the choroid must be understood as a trophic change, is by far preferable to Siegrist's assumption that actual tearing of some of the ciliary arteries has taken place, and is, furthermore, in accord with the more recent views on traumatic arterial spasm. Foisie [13] recognized that persistence of a relatively low grade arterial spasm is likely to cause nutritional changes, which ultimately may prove

12. Hudelo, Guillaumat and Maussion: Choroïdite arciforme traumatique (affection connue sous le nom de déchirure de la choroïde), Arch. d'opht. **5**:44-50, 1945.

13. Foisie, P. S.: Traumatic Arterial Vasospasm, New England J. Med. **237**:295-302 (Aug. 28) 1947.

detrimental to the functions of the affected organ. "An impaired arterial blood supply due to a subacute arterial spasm is regarded as the fundamental cause of much disability not inherent in the original injury." Traumatic arterial spasm occurs especially when areas in which decompression proceeds only slowly are exposed to concussion.

According to Ochsner,[14] vasoconstriction of the peripheral arteries is a protective mechanism. The degree of vasospasm, however, varies from one person to another, and with changing conditions: It may be so slight as to produce few, if any, manifestations, or it may be so severe as to assume the character of "local shock," and lead to ischemia and resulting gangrene.

Vasoconstriction due to ocular contusion was described by Harrington[15] as the cause of traumatic retinopathy. When a segment of the autonomic nervous system is exposed to shock, the chemical control of the vessels in the affected region of the eye is disturbed. Histamine-like substances are liberated, producing local dilatation, as well as increased permeability of the capillary walls. Even though Harrington's cases were obviously selected with a view to retinal changes, traumatic choroiditis was mentioned as an associated lesion in 1 instance of contusion retinopathy.

In summarizing these more recent observations, it may be stated that, conceivably, an indirect injury to the eye may affect those efferent nerves which control growth and nourishment. Inhibition of the essential functions of a trophic nerve will result in necrosis of the tissue normally supplied by it. The important factor is the change within the vessel wall, caused by traumatic disturbance of ocular innervation. Primary spasm increases permeability, and secondary dilatation accelerates the escape of blood into the tissues. The characteristic finding of hypotony following contusion of the eyeball suggests interference with the balance of regional secretions, due to an innervational disturbance. The metabolic processes within the tissues are regulated by trophic nerve fibers. More than a century ago, Magendie[16] established the observation that destruction of the fifth nerve causes degeneration of ocular tissues. It was this discovery which gave rise to the assumption that trophic fibers are associated with sensory nerves.

It has long been known that the capillaries are capable of active contraction. Duke-Elder[17] pointed out that the underlying mechan-

14. Ochsner, A., cited by Harrington.[15]

15. Harrington, D. O.: The Autonomic Nervous System in Ocular Diseases, Am. J. Ophth. **29**:1405-1425 (Nov.) 1946.

16. Magendie, F.: De l'influence de la cinquième paire de nerfs sur la nutrition et les fonctions de l'oeuil, J. de physiol. expér. **4**:176, 1824.

17. Duke-Elder, S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 1, p. 415.

ism may be a response either to nervous or to chemical stimulation. The former reaction is brought into play as a result of trauma to the globe. The existence of vasoconstrictor nerves throughout the sympathetic nervous system has been established. Sympathetic fibers extending into the uveal vessels have been demonstrated, and there can be no doubt that these fibers may cause constriction of the vascular structures of the fundus of the eye.

Vascular reflexes may be produced by locally circumscribed stimulation. A response limited to a restricted area may be brought about by a trophic irritant through reflexion ("short circuiting") of the impulse at the proximal point of division, within the neural tissues of the eye, the so-called axon reflex. Whenever function of the trophic fibers is inhibited, tissue necrosis results as a consequence of inadequately regulated nutrition.

There has not yet been established any unanimity of opinion concerning the finer details of the manner in which trophic changes in the choroid are produced. It can, however, no longer be doubted that choroidal lesions developing subsequent to indirect trauma to the eyeball represent tissue necrosis rather than actual disruption. Once this hypothesis has been accepted, it follows that the extent and distribution of the lesion must depend on the histologic peculiarities of the choroid in each case. Thus, the involved area does not necessarily have to assume an arcuate form but may exhibit, for instance, an irregular maplike aspect, sharply defined, of yellowish tinge and covered with a thinly scattered, diffuse pigmentation; or it may be a small, discrete lesion, irregular in outline, or oval with clearly circumscribed edges, but always pigmented to varying degrees. Osterberg [18] reported 4 cases in which the choroidal lesions could have been produced only in this manner.

PATHOLOGY

Wolff [19] gave a general description of the typical histologic changes observed in cases of so-called rupture of the choroid. A number of choroidal vessels, especially the smaller ones, have disappeared. Irregular distribution, as well as proliferation, of pigment is the rule. The retina overlying the affected area of the choroid is atrophic, and degeneration is apparent in its various layers. Proliferation of neuroglia, wandering of pigment and formation of new vessels are encountered.

18. Osterberg, G.: Three Cases of Acute Traumatic Chorioretinitis (Siegrist): One of Them Histologically Examined, Acta ophth. **14**:460-470, 1936.

19. Wolff, E.: Pathology of the Eye, Philadelphia, The Blakiston Company, 1935, p. 149.

Histopathologic observations were reported in greater detail by three other investigators. Hagedoorn [20] encountered a rupture, measuring 1.5 by 3 mm., near the ora serrata. At least the posterior elastic layer of the lamina basalis (Bruch's membrane), but probably the lamina in its entirety, was of normal appearance. It seemed not improbable that the anterior layer of the lamina basalis had been ruptured, but this could not be definitely ascertained because the sections were rather thick. The elastic posterior layer of the lamina basalis could be clearly identified and was completely normal, but a slight degree of lymphocytic infiltration was observed in the stroma of the choroid. In the areas of rupture, scar tissue was encountered, which was chiefly mesodermal in character, and was surrounded by ectodermal (glial) tissue, fixing the retina to the lamina basalis at the site of rupture.

Subsequent to accidental injury, Tillema [21] observed an abundance of hematogenous pigment, as well as conspicuous scar tissue formation, in the inner layer of the sclera.

Osterberg [18] reported interesting microscopic observations in a case in which the trauma responsible for the lesion had occurred thirty-five years previously. It was apparent that two regions of the choroid were involved, whereas only one rupture in the vicinity of the papilla had been noted at the time of clinical examination. Microscopically, choroid and retina showed extensive changes and were thinned. The larger vessels of the choroid, as well as the ciliary vessels, presented thickening of the adventitia and the tunica media, combined with scanty immigration of cells into the connective tissue of these layers and fraying of the elastic tissue of the media. Osterberg stressed that such changes neither prove nor disprove the theory of tearing of the ciliary vessels.

REPORT OF CASES

Ten cases of contrecoup injury to the eyeball are reported. In 5 instances the lesion in the fundus was more or less crescent shaped, while the patterns in the remaining 5 cases were atypical, ranging from a small, irregular pigmented spot to a large, maplike area of choroidal destruction. These cases are representative of the various forms in which lesions of the vascular coat are encountered after nonpenetrating trauma to the eyeball.

CASE 1.—L. P., a Negro woman aged 29, reported that seven years before admission she had been hit by a bottle in the left eye. Vision was 20/200, unimproved with correction.

20. Hagedoorn, A.: Choroidal Tears, Am. J. Ophth. **20**:13-15 (Jan.) 1937.

21. Tillema, A.: Atypical, Indirect, Incomplete Rupture of the Sclera, Brit. J. Ophth. **20**:193-198 (April) 1936.

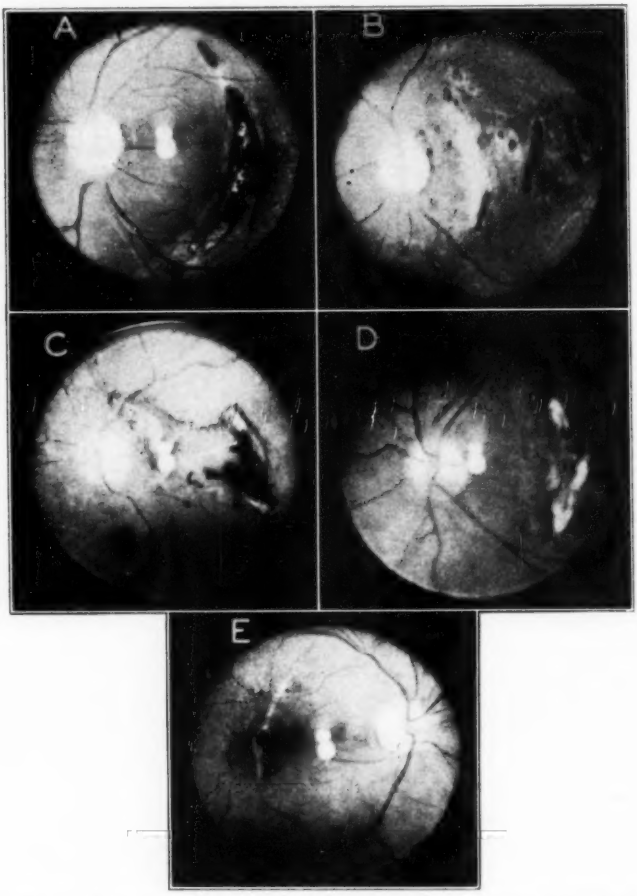

Fig. 1.—*A*, an extensive lesion in the temporal region, involving the macular area and concentric with the margin of the disk. The sclera is exposed in the central portion of the rent; the remainder is filled with masses of pigment.

B, four areas of rupture within a zone temporal to and concentric with the disk. In a circular region the retinal pigment has been partially absorbed.

C, two conspicuous breaks and a number of irregularly shaped fissures. All these lesions are concentric with the margin of the disk. Pigment covers the greater part of the hiatus.

D, a single break temporal to the macula with a pigmented area in its central portion.

E, concentric with the disk, a linear laceration in the macular region with a patch of pigment below its central portion. Temporally, another smaller linear rent is seen.

Examination of Fundus (fig 1 A).—An unusually extensive lesion of the choroid was observed in the temporal region of the fundus, and involving the macular area. The break in the continuity was concentric with the margin of the disk; the central portion was wider and somewhat elevated, while the lesion tapered off at both ends. Evidently the retina was not injured, the retinal vessels passing uninterruptedly across the break. On both sides of the lesion, however, the retina was darkened by dustlike deposits. Islands of exposed sclera were apparent in the central portion of the choroidal rent, whereas the remainder of the lesion was filled with solid masses of pigment.

CASE 2.—R. S., a youth aged 15, had been hit in the left eye with a baseball two years previously. Vision in that eye was limited to perception of light.

Examination of Fundus (fig. 1 B).—Four areas of rupture could be distinguished within an extended zone temporal to the disk. Surrounding the papilla, a large circular region was visible, in which the retinal pigment had been partially absorbed. The lesion nearest the disk was concentric with the margin of the disk, being wider in the central portion and tapering toward the ends. Above and temporal to this central area of rupture, two smaller areas of choroidal destruction were discernible, obviously the terminal portions of a second break, connected by tissue of normal appearance. Still closer to the periphery two shorter rents appeared, connected horizontally so as to assume approximately the shape of the letter H.

CASE 3.—J. S., a man aged 21, had injured his left eye with a baseball six years previously. Vision in that eye was limited to perception of light.

Examination of Fundus (fig. 1 C).—There appeared two conspicuous breaks in the choroid, as well as a number of irregularly shaped fissures in the horizontal direction, seemingly joining the two main breaks. All these lesions were situated in a field concentric with the margin of the disk. The retina vessels had not been interrupted in their course over the choroidal gap. More peripheral to the papilla, large masses of pigment covered the greater part of the hiatus, while closer to the margin of the disk only faint deposits of pigment appeared at the borders of the lesion.

CASE 4.—D. M., a man aged 26, had been hit in the left eye with a stone when he was 8 years old. Vision without correction was 20/25—.

Examination of Fundus (fig. 1 D).—A single break was seen somewhat temporal to the macula. Wider in the center, the rupture tapered at both ends. In the central portion of the white lesion, a pigmented area extended into the adjacent region on the nasal side, covering the upper terminal end of the rupture like a hood.

CASE 5.—E. G., a man aged 39, had been hit in the right eye with a piece of wood about twelve years previously. Vision with correction was 20/30—.

Examination of Fundus (fig. 1 E).—In the region of the macula was seen a linear laceration of the choroid, with a black patch of pigment a little below its central portion. The fissure extended along a line concentric with the disk. The retinal vessels continued over the laceration without interruption. Temporal to this break in the choroid, another, much smaller, linear area was observed, apparently representing a minute rupture of the vascular coat.

CASE 6.—W. C., a man aged 21, had been hit in the left eye with a clod of dirt six years previously. Vision was 20/100, unimproved with correction.

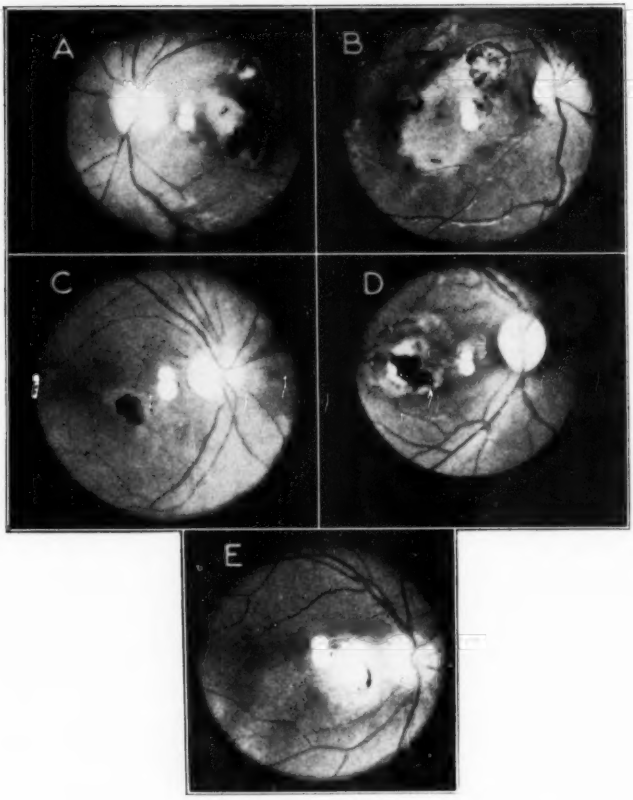

FIG. 2.—*A*, a broad, curved area in the region of the macula. The upper end is rounded; the lower, heavily pigmented and bifurcated. Below and temporal to the disk, two small concentric rents are seen in the choroid.

B, depigmented retina and atrophic choroid in a large area on the temporal side. The upper portion of the area shows a circular zone of pigmentation; below and temporally, a smaller, heavily pigmented lesion is seen.

C, an oval, heavily pigmented patch in the macular region. The sclera can be seen in spots. A narrow border of flocculent masses is visible in the superior and temporal directions.

D, an irregular, deep lesion involving the macula and a large adjacent area. The central portion is heavily pigmented and encircled by a whitish zone of exposed sclera. A large, cloudy region of choroidal and retinal atrophy extends nasally and temporally.

E, a depressed, oval area, temporal to the papilla. Except for a thin pigmented rim, the lesion is white and surrounded by a ring of cloudiness.

Examination of Fundus (fig. 2 A).—A broad, curved area was present in the region of the macula. The retinal vessels passed over the gap without interruption. The upper end of the break was rounded; the lower extremity, bifurcated. In the lower portion of the lesion appeared a dense, dark area of pigment, while the upper third was much paler. Below, and temporal to, the disk two small concentric fissures were observed, being apparently slight rents in the choroid.

CASE 7.—M. S., a youth aged 17, had been hit in the right eye with a BB shot. Vision amounted to counting of fingers at 1 foot (30 cm.).

Examination of Fundus (fig. 2 B).—Depigmented retina and atrophic choroid occupied a large, irregular area on the temporal side of the eye, including the macular region. In the upper portion of the area, a circular patch of mottled pigmentation, about the size of the disk, was observed. Below and temporal to this area, another, but smaller and more heavily pigmented, lesion could be seen. The retinal vessels were of normal appearance and passed uninterruptedly over the choroidal lesions.

CASE 8.—D. B., a man aged 67, had been hit in the right eye with an apple at the age of 17. Vision was limited to perception of light.

Examination of Fundus (fig. 2 C).—Retinochoroiditis of long standing appeared in the form of an approximately oval patch in the macular region. This depressed area was heavily pigmented, but the sclera could be seen in small spots throughout the zone of pigmentation. This zone was surrounded by a narrow border of small, flocculent masses, containing a number of grayish dots of irregular shape, jutting out pointlike in the superior and temporal directions.

CASE 9.—T. J., a youth aged 16, had been hit in the right eye with a ball two years previously. Vision was 20/200, unimproved with correction.

Examination of the Fundus (fig. 2 D).—An irregular, deep lesion involved the macula and a large adjacent area. The sharply demarcated defect was heavily pigmented in its central portion and was encircled by a whitish zone in which the sclera was exposed. Surrounding the white scleral border a large, irregular, cloudy area of choroidal and retinal atrophy extended almost to the disk on the nasal side and to the equator on the temporal side.

CASE 10.—B. F., a man aged 59, gave a history of injury to the right eye with a hard object during the first world war. Vision amounted to 20/200, unimproved with correction.

Examination of the Fundus (fig. 2 E).—A depressed, oval area, somewhat larger than the disk, appeared just temporal to the papilla. Except for a thin pigmented rim at the nasal edge, the lesion was entirely white, owing to exposure of the underlying sclera. The rent in the retina and choroid was surrounded by a ring of cloudiness, blending on the temporal side into another nebulous area, which, in turn, extended to the equator. The retinal vessels were unaffected, passing uninterruptedly over the lesion.

COMMENT

In the cases described here the choroidal lesions presented a great variety of shapes, as well as sizes and positions. A search of the literature revealed no arcuate rupture of the choroid as large as the one in figure 1 *A*. It is of interest to note that, although in this case the extensive lesion involved the macular area, vision still amounted to 20/200.

In 2 other cases vision was almost normal: 20/25 — in case 4 and 20/30 — in case 5. Cases 2 and 3 constitute good examples of multiple ruptures.

Except for the differences in shape and position, all lesions presented similar characteristics. Necrosis and atrophy of the choroid were encountered in all instances. No essential dissimilarity could be detected which would have warranted a distinction between typical, i.e., arcuate and concentric, and atypical morbid changes on any basis other than the obvious discrepancy in shape and position. This essential similarity of lesions of different appearances was confirmed by the results of microscopic examination. In at least 1 instance [18] a second, diffuse, area, of irregular shape, was discovered by microscopic examination at autopsy in an eye in which only one central lesion, adjacent to and concentric with the papilla, had been observed clinically. The form of the lesion in a specific instance—whether crescent shaped or irregular—depends on the portion of the fundus involved, as well as on the structure and composition of the tissues.

From the observations in the present cases, as well as from an appreciation of the etiologic factors in these lesions, it may be suggested that the discontinuity of the choroid following nonpenetrating injury to the globe, formerly regarded as actual rupture, presents in fact necrotic changes, evidently of trophic character. The term "rupture of the choroid" is misleading, and lesions of this kind should henceforth be classified exclusively as traumatic choroiditis. Even though the character of these choroidal changes is not influenced by their shape, position or pattern, the pronounced difference in appearance suggests distinction between the two typical forms which this disease entity may assume. Whenever the lesion is concentric, the term arciform traumatic choroiditis is appropriate; in all other instances it should be designated as diffuse traumatic choroiditis.

SUMMARY

Ten cases of so-called rupture of the choroid are reported.

The etiology and pathology of these lesions are discussed.

Discontinuity of the choroid following indirect injury to the eyeball is due to necrotic changes of trophic character.

A more precise terminology is proposed; arciform traumatic choroiditis is suggested as a better name for lesions of concentric shape, and diffuse traumatic choroiditis, for those of irregular outline.

610 South Broadway (14).

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Sixteenth International Congress of Ophthalmology.—The Sixteenth International Congress of Ophthalmology will be held in London, July 17 to 21, 1950. This is the first International Congress to be held for thirteen years. Any qualified medical practitioner may become a member of the Congress; others who are not so qualified but who have rendered service to ophthalmology and who are approved by the International Council of Ophthalmology will be eligible to attend. Relatives and friends of members will be welcomed as associate members and will be eligible to attend the opening and closing ceremonies and all social functions. The three official languages of the Congress are English, French and Spanish; any language, however, may be used. The subjects to be discussed are: (1) the role of the sympathetic system in the genesis of vascular hypertension and its effect on the eye, and (2) the clinical and social aspects of heredity in ophthalmology. Those who desire to participate in the main discussions or in reading communications on other ophthalmologic subjects are requested to communicate with Mr. Keith Lyle, International Congress of Ophthalmology, 45 Lincoln's Inn Fields, London, W.C.2.

Communications should not be longer than 2,500 words and will be read in abridged form, for which the author will be allowed ten minutes. On their submission, they should be accompanied with résumés, 250 words in length, in the three official languages. As the number submitted may be greater than can be accommodated, the publications committee reserves the right of rejection. No guarantee can be given that any paper will be included in the official report of the Congress unless it is received six months before the date of the meeting (i. e., by February 1950). Scientific demonstrations will be arranged, and there will be scientific and industrial exhibitions. Contributions to all of these will be welcomed.

Further details, including information on the social program, will be published from time to time.

Symposium on Strabismus.—A symposium on strabismus will be held at the State University of Iowa College of Medicine, May 22 through 28, inclusive. In addition to the staff of the department of ophthalmology of the university, the following guest lecturers will participate in the symposium: Dr. Walter B. Lancaster, Boston; Dr. Francis H. Adler, Philadelphia; Dr. George P. Guibor, Chicago; Dr. Walter H. Fink, Minneapolis; Dr. Kenneth C. Swan, Portland, Ore.; Dr. Richard G. Scobee, St. Louis; Dr. Frank D. Costenbader, Washington, D. C.; Dr. Harold W. Brown, New York; Dr. Hermann W. Burian, Boston.

Further information regarding the course may be obtained from Dr. James H. Allen of the department of ophthalmology, State University of Iowa College of Medicine, Iowa City.

The course will be limited to twenty-five physicians, and the registration fee for the course will be $150.

Annual Examination for Orthoptic Technicians.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in September and October 1949.

The written examination will be nonassembled and will take place on Thursday, Sept. 8, 1949 in certain assigned cities and offices and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, October 8, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the secretary of the American Orthoptic Council, Dr. Frank D. Costenbader, 1605 Twenty-Second Street, N. W., Washington 8, D. C., and must be accompanied with the examination fee of $25. Applications will not be accepted after July 1, 1949.

The American Board of Ophthalmology.—The American Board of Ophthalmology wishes to announce that it does not evaluate, approve or disapprove any ophthalmic residency toward fulfilling the requirements of candidates for board examinations. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the booklet of information will be accepted. A copy of this booklet can be obtained from the secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

SOCIETY NEWS

Pennsylvania Academy of Ophthalmology and Otolaryngology.—The annual meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held April 22, 23 and 24, 1949 at the Penn Harris Hotel, Harrisburg, Pa.

Among the speakers who will present papers at this meeting will be Drs. A. D. Ruedemann, J. R. Lindsay, R. O. Rychener, C. S. Nash, J. G. Linn, Arno Town and G. M. Coates.

In addition to formal presentations, the meeting will include a round table discussion on "Headache," participants in which will include representatives of all major specialties; and there will be a study club to discuss "Cataract Problems," the discussers to include Drs. Ruedemann, Rychener and Town.

Sociedad Nicaragüense de oftalmología.—The Sociedad Nicaragüense de oftalmologia was founded on Nov. 8, 1948. The following officers were elected: president, Dr. Victor M. Godoy; vice president, Dr. Salvador Reyes; secretary, Dr. E. Alvarez Montalvan; treasurer, Dr. Ricardo Lacayo; vice treasurer, Dr. Adan Fuentes S.; voting representatives, Dr. Adan Fuentes S., Dr. Juan Derbishire and Dr. Penciano Munox; delegate of Nicaragua to the Pan-American Congress of Ophthalmology, Dr. Ricardo Lacayo.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

AN ANALYSIS OF FIBRE-SIZE IN THE HUMAN OPTIC NERVE. L. W. CHACKO, Brit. J. Ophth. **32:** 457 (Aug.) 1948.

The specimen used was the optic nerve of a man aged 61 who had no record of any disturbance of the visual system. The stain and the technic employed in measuring the diameter of the fibers are described. The results obtained show that the human optic nerve contains fine, closely packed myelinated fibers without Schwann sheaths; these fibers exhibit a continuity in range of diameter, from the minimum of 0.7 micron to the maximum of 8.0 microns, and occasionally 10.0 microns. The histogram shows that the largest number of fibers is under 1.0 micron in diameter, and the next largest from 1.0 to 2.0 microns, at which level the frequency drops rather steeply toward the base line and then more gradually in the direction of the larger fibers, with an indication of a second low rise in the region of the fibers 5.0 to 7.0 microns in diameter. The last feature was more pronounced in confirmatory measurements carried out from other preparations. Minute "dots and rods," mentioned by Brodal and Harrison (1948) as indicative of the possible existence of minute myelinated fibers in the central nervous system, were not particularly evident in any of the author's preparations, although their presence could not positively be excluded. Moreover, the continuous range that characterizes diameters between 0.7 and 8.0 microns did not extend below the 0.7 micron diameter down to the sizes indicated by "dots and rods" that may be present. The total number of optic fibers in the human optic nerve was estimated to be between 815,000 and 1,000,000. W. ZENTMAYER.

Aqueous Humor

ON THE TYNDALL PHENOMENON IN THE ANTERIOR CHAMBER. A. HUBER, Ophthalmologica **114:** 228 (Oct.-Nov.) 1947.

In this article a method is described for quantitative measurement of the Tyndall effect in the anterior chamber, with the hope that the method may be useful in clinical practice. F. H. ADLER.

STUDIES ON THE EFFECT OF CERTAIN STIMULANTS ON THE ACCOMMODATION OF THE EYE AND OF THE THRESHOLD VALUE FOR THE EFFECT OF VITAMIN B_1 ON THE ACCOMMODATION. B. KNAPE, Acta ophth. **26:** 35, 1948.

The investigations described in this paper show that certain substances of a generally stimulating nature increase ocular accommodation. Such results were obtained with desoxyephedrine ("pervitin") (2 tablets by mouth) and with 5 cc. of nikethamide injected intramuscularly. Similarly, it was shown that the accommodative mechanism is very

sensitive to thiamine hydrochloride, injected intravenously. It appears that between 2 and 5 mg. of the vitamin is necessary to produce an effect.

O. P. PERKINS.

Conjunctiva

PIGMENTATION OF THE PALPEBRAL CONJUNCTIVA RESULTING FROM MASCARA. A. B. REESE, Am. J. Ophth. **30:** 1352 (Nov.) 1947.

Reese describes a granular, stippled pigmentation of the palpebral conjunctiva of the upper lids near the upper border of the tarsus. From the available data, he concludes that this is due to mascara together with some factor peculiar to the patient determining its occurrence.

W. S. REESE.

RICKETTSIAL BODIES IN EPIDEMIC NUMMULAR CONJUNCTIVITIS (EPIDEMIC KERATOCONJUNCTIVITIS). G. L. COLUMBO, Ann. d'ocul. **180:** 470 (Aug.) 1947.

The author prefers the name "epidemic nummular conjunctivitis" as more descriptive of the disease process. He feels that the laboratory identification of rickettsial bodies can be made readily with his technic, especially if fresh infections are seen. The clinical diagnosis can be made on the basis of the objective and subjective symptoms, before the typical corneal lesions are visible. The method of obtaining scrapings and their identification is described. The author believes that the microscopic cells he describes can best be termed "rickettsoides."

The significance of inclusion bodies is discussed. The inclusion bodies described differ from those appearing in trachoma and inclusion blennorrhea. Final confirmation that this disease is caused by a virus will depend on filtration and transmission experiments. The author believes that a virus is the etiologic agent for the following reasons: 1. The conjunctival exudation is formed exclusively by small mononuclear cells, which are found in other conjunctival diseases caused by a virus. 2. The presence of rickettsoid bodies in numerous cases of epidemic nummular conjunctivitis.

P. R. MCDONALD.

Congenital Anomalies

THE MARCUS GUNN PHENOMENON. E. B. SPAETH, Am. J. Ophth. **30:** 143 (Feb.) 1947.

Spaeth reports 4 cases of jaw winking and discusses the pathologic process and the theories explaining it. He stresses the importance of ophthalmic surgery for the condition and feels that the intracranial approach is not necessary.

W. S. REESE.

DISCOVERY AND HISTOPATHOLOGIC STUDY OF A CASE OF CHOROIDEREMIA. E. FORNES PERIS, Arch. Soc. oftal. hispano-am. **7:** 134 (Feb.) 1947.

The author was requested to make a histopathologic examination of the eyes of a 2 month old infant who died of a condition diagnosed as malnutrition and presented corneal lesions presumably produced by avitaminosis.

To the surprise of the examiner, it was found that the choroidal layer of the globe was absent. Except for the pathologic condition of the cornea, which consisted of infiltration and ulceration produced by lagophthalmos, the histologic structure of the eyes was normal, save for the absence of the choroid in both eyes. There was no other congenital malformation. The only separation of the sclera from the retina was a layer of polyhedral cells with heavy pigmentation, which exhibited the characteristics of retinal, not choroidal, pigment.

The article is illustrated with photomicrographs.

H. F. CARRASQUILLO.

Cornea and Sclera

RESULTS OF PLESSIOTHERAPY FOR CORNEAL DISEASES. R. GALLENGA and A. ROSSI, Rassegna ital. d'ottal. **13: 7**, 1946.

The authors applied plessiotherapy according to the method of Chaoul for numerous superficial corneal diseases, which, in contrast to the deep lesions, are notoriously insusceptible to ordinary roentgen therapy.

Good results were obtained with herpetic keratitis, recent corneal leukoma, peripheral corneal ulcer and acute catarrhal conjunctivitis. Old or recent corneal vascularization of pannus regresses. In addition, it accelerates the return of corneal sensitivity; it does not induce any obvious ocular reaction aside from a variable amount of hypotony, which produces no disturbance even when it persists for some time.

The authors recommend that plessiotherapy not be reserved for the more serious cases and emphasize that early treatment has great value in cases of corneal disease, especially when the necessity for transparency obtains after clinical healing has occurred.

G. B. BIETTI—Translated, J. J. LO-PRESTI.

THE PATHOLOGY AND THERAPY OF FISTULA OF THE CORNEA. A. W. MULOCK HOUWER, Ophthalmologica **113:** 309 (May) 1947.

Fistula of the cornea is the safety valve mechanism of an eye in which glaucoma has developed as the result of a perforating corneal ulcer. The methods of treating this condition published prior to 1940 have given unsatisfactory results; these the author believes are due to their being based on a wrong construction of the cause of fistula of the cornea. He recommends cyclodialysis in cases of this defect of the cornea, for fistula can be closed only by first curing the glaucoma.

F. H. ADLER.

Experimental Pathology

EXPERIMENTAL OBSERVATIONS ON THE INTRA-VITREOUS USE OF PENICILLIN AND OTHER DRUGS. J. P. DUGUID, M. GINSBERG, I. C. FRASER, J. MACASKILL, I. C. MICHAELSON and J. M. ROBSON, Brit. J. Ophth. **31:** 193 (April) 1947.

Ophthalmologists, understandably, are hesitant to inject drugs intravitreously on account of the possible damage to the vitreous gel, the retina and other structures. In the present experiments, without use of surface diathermy, a small needle could be introduced into the vitreous

and a small quantity of saline solution injected without any ill effects. With the exception of pure penicillin, all the drugs introduced into the vitreous, including impure penicillin, were highly damaging to the retina, to a degree which excluded their use clinically. Pure penicillin in some cases was shown to cause small areas of retinal damage, but slight by comparison with the effect of impure penicillin or any of the other drugs. Under favorable conditions, penicillin introduced by this means is highly effective in the control of infections of the vitreous body, and the diffusion experiments demonstrate that the drug diffuses but slowly from the vitreous, thus maintaining a chemotherapeutic concentration for two or three days after a single injection, in contrast to its rapid disappearance when injected into most other tissues in the body. In cases in which an eye is seriously endangered by infection in the vitreous, it appears justifiable to consider the use of pure penicillin by intravitreous injection, the control of the infection more than outweighing the possibility of small areas of retinal damage. If doses comparable to those used in the experiments are given, it would appear sufficient to repeat the injections at intervals of two or three days, the slow diffusion from the vitreous permitting a therapeutic level of the drug to remain for that time.

W. ZENTMAYER.

General

OPHTHALMOLOGY AND AVIATION. A. MERCIER, Arch. d'opht. **6:** 413, 1946.

This paper consists in a review of the work which has been done in connection with ophthalmology and aviation. The author divides the paper into several different topics and refers especially to the work in the visual fields as shown by Livingston. He also refers to the effect of altitude in relation to the visual function and calls attention to the work which has been done in relation to night flying. An extensive bibliography is appended.

S. B. MARLOW.

RECENT EXPERIENCES WITH THE USE OF CONTACT GLASSES. G. MIHALYHEGYI, Ophthalmologica **114:** 159 (Sept.) 1947.

The author finds that when a contact glass is not pressing on the eyeball an air bubble introduced collects on the upper corneal margin when the patient is looking straight ahead. When the patient is looking sideways, the bubble goes to the opposite side. If the lens is pressing on the eyeball, the air bubble varies from the described positions. The author cites the advantages and disadvantages of plastic and glass contact lenses. Plastic lenses do not break easily when dropped, but they have certain disadvantages. They are more easily produced, but the grinding of the optical surface is more difficult. They scratch more easily than glass lenses, and therefore they need frequent polishing. They may become opaque, and nearly every chemical substance with the exception of benzine damages them. The glass lens, on the other hand, has only one disadvantage; it breaks when dropped.

F. H. ADLER.

General Diseases

SOME VULGAR ERRORS IN REGARD TO GOITRE. J. W. LINNELL, GEOFFREY KEYNES and J. E. PIERCY, Brit. M. J. 2: 449 (Sept. 26) 1946.

As ophthalmologists frequently encounter cases of thyroid disorders, this article, presenting the surgical point of view, will be found valuable and instructive. The authors begin by stating that it is not true that comparatively few goiters become toxic; it is now believed that over 50 per cent become toxic if left untreated. It is rare that when early middle life is reached the goiter does not show evidences of associated toxicity. Aside from the gross symptoms, those of lesser degree are important. They can be detected only on careful examination, and they may amount to no more than some of the following: lassitude; minor or occasional palpitations; slight irritability or emotional instability; loss of weight; irregular sweating or feelings of heat; a small rise in the resting or, better, sleeping pulse rate; a fine digital tremor; the suspicion of a stare, due to retraction of the upper lids, and an almost imperceptible difference in the width of the palpebral fissures. Next to acute rheumatism, toxic goiter is the most fruitful cause of auricular fibrillation, and goiter of apparently mild toxicity is frequently responsible for it. Once the auricular fibrillation is established, it may be a forerunner of congestive failure.

With regard to the carcinomatous changes, neither the size of the goiter nor the age of the patient mattered, and of single nontoxic nodules 24 per cent showed this change. The goiters, particularly of the nodular type, are apt to cause symptoms of pressure on the trachea. While the cardiovascular, nervous and metabolic systems are all affected in cases of toxic goiter, sometimes only one or two of these systems may be affected to any notable degree. It is not infrequent to find patients with classic symptoms of toxic goiter in which the heart rate is but slightly increased. Maintenance, or even an increase, of weight is not uncommon in these patients. The basal metabolic rate, while it is the best laboratory test, according to Joll was a "poor best," and the authors emphasize that with a large and important group of goiters in which the toxicosis is minimal the danger of eventual auricular fibrillation is real; so little is the general metabolism affected that it is rare to find the basal metabolic rate raised.

The beneficial results of iodine are only temporary, and its use should be restricted to the period immediately preceding or immediately following operation.

Roentgen therapy is of no value for nodular toxic goiter. The claims for thiouracil have been excessive, and it is most valuable in preparation for the operation. While it has been believed that patients with auricular fibrillation and gross signs of congestive failure are too ill for operation, the authors have seen scores of patients who have come safely through the operation and have enjoyed reasonable health for years thereafter. The results of subtotal thyroidectomy are regarded by thyroid surgeons to be most satisfactory. Joll found that 90 per cent of patients were able to return to active life. In the hands of the expert surgeon, especially if he is a member of a trained team, the mortality for even toxic goiter is approximately 1 per cent. With the judicious use of thiouracil, patients with profound thyrotoxicosis achieved a degree of

preoperative improvement. The resulting vascularity can be greatly reduced by discontinuing the remedy for two to three weeks before the operation and substituting iodine. While the technical difficulties are generally few, there is an important minority of cases in which such difficulties are real. An experienced anesthetist is especially needed, and the authors think that patients with goiter should be treated in goiter clinics.

The authors conclude that, in view of the many dangers which beset it, every nodular goiter should be removed surgically without undue delay.

ARNOLD KNAPP.

Glaucoma

THE THALAMUS AND GLAUCOMA. A. MAGITOT, Ann. d'ocul. **180:** 1 (Jan.) 1947.

The author states that, despite sixty years of research, glaucoma is still the number 1 enemy in ophthalmology. Recently, considerable attention has been paid to gonioscopic examination of the angle of the anterior chamber. Several factors are recognized in this disease. First, glaucoma is a disease, and the increase in ocular tension is but a symptom. Magitot points out that one sees patients with all the signs and symptoms of glaucoma except for increased tension. There are also patients whose tension has been controlled by operation without alleviation of the disease. The author also points out the great variability in individual tonometers and in the elasticity of the sclera. This variability leads him to conclude that the tonometric reading itself is not the significant factor, but that all the other signs, such as bedewing of the cornea and changes in the fields, must be taken into account. Second, the circulatory mechanism in glaucomatous eyes is characterized by an increase of the venous pressure. The arterial pressure is also raised. Even if the tension is normalized, the capillary circulation is still not normal. This disturbance in the capillary circulation is not limited to the eye in glaucomatous patients. Third, there is some dysfunction of the endocrine glands in patients with glaucoma. It is difficult to determine the exact nature of these endocrine disturbances, since the laboratory tests are not accurate. Fourth, there is a disturbance in the vegetative nervous system. There is some question whether there is a decrease or an increase in sympathetic tone. This may account in part for changes in the capillary circulation. Fifth, the neuropsychiatric angle must be considered. Reference is made to a previous paper of the author's and to a paper of Schoenberg's on this phase of the subject. Many glaucomatous patients are hypersensitive to pain, thermal changes and other sensory stimuli. The author discusses this phase at considerable length and points out that in the central nervous system the thalamus is the "affective" center. The vegetative nervous system is closely linked with the thalamus. The paper closes with a plea for consideration of other than merely the medical and surgical care of the eyes. Glaucomatous patients may need psychiatric care; they should lead a comparatively regulated life, and sedatives may be indicated to relieve an irritable diencephalon.

P. R. MCDONALD.

CHRONIC GLAUCOMA AND MINIMAL ELECTIVE VASODILATATION. JEAN GALLOIS, Ann. d'ocul. **180:** 20 (Jan.) 1947.

The author believes that the state of the choroidal and retinal vessels plays an important part in the genesis of chronic glaucoma. He points out that glaucomatous patients frequently manifest peripheral vascular disorders. In glaucomatous patients involvement of the choroidal veins frequently occurs. The author refers to previous reports on the use of acetylcholine in treatment of chronic glaucoma. In some cases the tension was lowered. In 1930 he reported a case in which he used acetylcholine; vision improved, but the tension was elevated. He stated the belief that the improvement of vision was due to improvement in the retinal circulation, whereas the tension was increased as a result of the vasodilatation of the choroidal vessels. The author has subsequently tried various vasodilator drugs in minimal doses, attempting to obtain the beneficial without the deleterious effects.

Acute glaucoma, glaucoma secondary to uveitis, hemorrhagic glaucoma and old glaucoma have by experience been proved unsuitable for this method of treatment. There are other conditions which do not respond to any therapy, and in a certain number of cases acetylcholine causes a rise in tension. The author does not recommend vasodilation as a routine treatment of glaucoma. If a therapeutic test shows that the tension is lowered, it is worth while to continue the therapy. The author has used various vasodilators but favors nicotinic acid (0.025 Gm. given by mouth).

P. R. MCDONALD.

IRIDENCLEISIS IN TREATMENT OF GLAUCOMA SECONDARY TO IRIDOCYCLITIS. MARCEL KALT, Arch. d'opht. **7:** 18, 1947.

The author describes his technic and reviews a series of 22 cases. In 86 per cent a definite lowering of the tension occurred; in 60 per cent there was improvement in the visual acuity; in 50 per cent the field of vision was maintained; in 59 per cent there was a recurrence of the initial iridocyclitis. These results have encouraged the author to use this procedure in primary glaucoma.

S. B. MARLOW.

Injuries

STATISTICAL STUDY OF FOUR HUNDRED AND EIGHTEEN PENETRATING WOUNDS OF THE GLOBE TREATED AT THE HOTEL DIEU BETWEEN 1940 AND 1945. P. DESVIGNES and C. BOUDON, Arch. d'opht. **7:** 28, 1947.

This paper is an extensive analysis of the authors' cases from the point of view of etiology, prognosis and treatment. In their observations, the nature of the traumatism was the most important factor in the prognosis. The corneal wounds furnish by far the greatest proportion of eyes with vision lower than 1/10; the corneoscleral wounds and scleral wounds in the ciliary zone, the greatest number with atrophic changes and mutilating interventions. The authors compare their observations with the statistics presented by other investigators. The use of the sulfonamide compounds has not been helpful in treatment of the conditions. They believe that it is possible to save a certain number of eyes which seem to be so badly damaged that return of

visual function is doubtful. The article is carefully compiled, so that an adequate abstract is difficult. It should be read in the original to be fully appreciated.

S. B. MARLOW.

Lacrimal Apparatus

DACRYOCYSTITIS OF INFANCY. J. V. CASSADY, Am. J. Ophth. **31:** 773 (July) 1948.

Cassady states that tears appear at the age of 3½ weeks and that the incidence of dacryocystitis in infancy is from 1.75 to 5 per cent. He believes that early probing of the nasolacrimal duct in infants is the method of choice and that it produces no untoward injury if done carefully and gently.

W. S. REESE.

TECHNIC OF APPLICATION OF SUTURES IN DACRYOCYSTORHINOSTOMY. N. MEDVEDER, Vestnik oftal. **24:** 41, 1947.

Medveder applies sutures to the nasal mucous membrane before making the incision. A probe is inserted into the middle meatus with the concave surface toward the mucous membrane, and three sutures are passed under the probe on each side of the mucous membrane. Then the probe is turned and the incision is made along its concave side. The rest of the operation is continued in the usual manner. This modification was found to simplify the operation in avoiding bleeding or tearing of the edges of the mucous membrane.

O. SITCHEVSKA.

Lens

INTRACAPSULAR CATARACT EXTRACTION AND DETACHMENT OF THE RETINA. S. SCHIFF-WERTHEIMER and J. SÉDAN, Ann. d'ocul. **180:** 513 (Sept.) 1947.

The authors carefully point out that they are not discussing the advantages of one type of cataract extraction over another. Neither are they presenting a large series of statistics on the incidence of detachment of the retina.

They believe that detachment of the retina following intracapsular cataract extraction occurs in about 1.25 to 1.35 per cent of cases. One of the first questions one asks is, "Is detachment of the retina after this procedure more frequent than after simple cataract extraction?" No definite statistics are available. The number of cases of retinal detachment seen in the hospitals has definitely increased since intracapsular cataract extraction has become popular. However, during the same period the surgical treatment of detachment has made rapid advances. Patients who previously would not have been admitted are now being treated surgically. Of all the complications following intracapsular extraction, detachment of the retina is one of the least frequent.

Do any conditions favor detachment of the retina in patients with total aphakia? The authors stated that in their series patients between 35 and 55 years of age, persons over 75 and myopic patients who had been operated on for cataract were more likely to have detachments of the retina. In the group with the so-called presenile cataracts, one might suspect that the zonule would be tougher and that the detachment

might be caused by the additional traction required to dislocate the lens. The authors feel that the precocious development of the cataract may be due to peripheral choroiditis and that this may predispose the eye to detachment of the retina. Cataract extraction in the aged is seldom accompanied with any complication, such as loss of vitreous. Predisposition to detachment in persons of this age group is due to degenerative vascular changes in the periphery of the choroid. The authors feel that extraction of a cataract in a myopic patient should be postponed as long as possible. In 2 patients of their series the eye not operated on was already blind from a detachment. Myopic patients are considerd poor risks for intraocular surgery.

Detachment of the retina following cataract extraction has always carried a poor prognosis. The authors feel that, as in the case of detachments associated with senility, the prognosis depends on the early recognition of the condition and on early operation. They believe that intracapsular cataract extraction is no more hazardous than a simple extraction, especially if one considers the complications that may follow discission of a secondary cataract. If a detachment does occur, one can see the fundus much better without cortical material in the pupillary space. Finally, it must be remembered that a detachment of the retina occurring months or years after the extraction of a cataract may be due to factors other than the aphakia.

P. R. McDONALD.

Lids

OPERATIVE PROCEDURE FOR ENTROPION OF THE UPPER LID. N. MARTIN AMAT, Arch. Soc. de oftal. hispano-am. **7**: 603 (June) 1947.

The author's method, applicable in cases of severe entropion, is as follows: (1) incision of the skin and orbicularis muscle the whole length of the lid, from the lacrimal punctum to the external commissure, and about 2 mm. from the line of the eyelashes; (2) resection of the fibers of the orbicularis muscle present in the wound and dissection of the superior cutaneomuscular plane to above the superior border of the tarsus (the lower plane, where the eyelashes are implanted, is not dissected); (3) section of the tarsal plate in all its length and thickness and about 1.5 mm. from the root of the eyelashes; (4) thinning of the tarsal plate (as it is usually thickened), this thinning being performed with a very fine knife; (5) insertion of the sutures and superposition of the ciliary border on the upper tarsal flap. Five sutures are usually employed to hold the ciliary border in this position, and fine silk and needle are to be used. The needle is introduced from behind the eyelashes, in the intermarginal line of the palpebral border, and is brought out behind the root of the cilia and in from the lower, narrow, band of the tarsus, where the cilia are implanted, to be again introduced through the upper band of cartilage and to come out a little above, through the tendon of the levator muscle. The sutures are tied, and the skin is left free without suturing.

The esthetic result, according to the author, is perfect.

The article contains drawings to illustrate the various steps in the procedure.

H. F. CARRASQUILLO.

TREATMENT OF ULCERATIVE BLEPHARITIS WITH GRAMICIDIN. A. PETROV, Vestnik oftal. **24:** 43, 1947.

Forty-five patients with severe ulcerative blepharitis were treated with a 4 per cent alcoholic solution of gramicidin daily for seven to ten days by application to the ulcerated lid margins. In 44 patients a cure was obtained in ten to eighteen days.

O. SITCHEVSKA.

Methods of Examination

THE SIGNIFICANCE OF THE INTRACUTANEOUS TEST FOR HYPERSENSITIVITY TO UVEAL PIGMENT. S. D. MCPHERSON JR. and A. C. WOODS, Am. J. Ophth. **31:** 35 (Jan.) 1948.

McPherson and Woods found clearcut positive reactions to intercutaneous tests for pigment hypersensitivity in cases of (1) sympathetic ophthalmia, (2) prolonged uveitis after injuries or operations involving the uveal tract and (3) the Vogt-Koyanagi syndrome. They conclude that a positive reaction occurring after an injury or operation involving the uveal tract should put one on guard for sympathetic ophthalmia.

W. S. REESE.

GONIOSCOPY. E. A. W. SHEPPARD and W. J. ROMEJKO, Am. J. Ophth. **80:** 159 (Feb.) 1947.

Sheppard and Romejko present a simple, low magnification method of gonioscopy which is of value to the beginner because of its greater ease of orientation. They state that the iridodonesis is more easily diagnosed by this method and that it should be used routinely in cases of glaucoma and intraocular surgery, both before and after operation.

W. S. REESE.

Neurology

ON THE MECHANISM OF PRODUCTION OF MASSIVE PRERETINAL HEMORRHAGE FOLLOWING RUPTURE OF A CONGENITAL MEDIAL-DEFECT INTRACRANIAL ANEURYSM. A. J. MILLER and J. T. CUTTINO, Am. J. Ophth. **31:** 15 (Jan.) 1948.

Miller and Cuttino report a case of preretinal hemorrhage following massive subarachnoid hemorrhage from the rupture of an aneurysm of the internal carotid artery due to a medial defect. They review prevalent theories of the mechanism of these preretinal hemorrhages and suggest that the hemorrhages result from sudden increase in preretinal intravenous pressure due to compression of the choroidal anastomosis of the central vein of the retina at the level of the lamina cribrosa, together with compression of the central vein at its intervaginal portion by extension of the subarachnoid hemorrhage into the intervaginal space about the optic nerve.

W. S. REESE.

TOXIC DISORDERS OF THE CHIASM. E. J. TRON, Vestnik oftal. **26:** 3, 1947.

Eight patients with acute methyl alcohol poisoning had involvement of the chiasm with severe reduction of vision as a result of atrophy of the optic nerves. Studies of the visual fields showed the presence of

hemianoptic central scotomas, mostly bitemporal, in 4 patients. The peripheral fields were normal. In the other 4 patients there was found a typical asymmetric partial binasal hemianopsia, usually combined with central scotomas. The character of the defects in the visual fields indicated the localization of the lesion in the chiasm as a result of its toxic involvement. Similar cases have not been reported in the literature. Tron believes that the involvement of the peripheral neuron of the visual tract in cases of methyl alcohol poisoning can affect either both optic nerves (the commoner) or the chiasm. In the 8 cases of methyl alcohol poisoning in a series of 35 cases with optic nerve atrophy, the chiasm was involved. It is possible that individual peculiarities in the blood circulation or of metabolism in certain sections of the peripheral neuron of the visual tract are responsible for the toxic products' being carried to the chiasm. Seven figures from visual field studies illustrate the article.

O. SITCHEVSKA.

Ocular Muscles

NONOPERATIVE TREATMENT OF CONCOMITANT STRABISMUS. SUZANNE BRAUN-VALLON, Ann. d'ocul. **180:** 391 (July) 1947.

The author reports her observations on the orthoptic treatment of strabismus as conducted in England and the United States. The indications for treatment and the various methods of treatment are described.

Orthoptic treatment is usually carried out in addition to operation. It does not bring about a rapid cosmetic result but is another stage of treatment in the attempt to obtain binocular vision.

P. R. MCDONALD.

UNDERCORRECTION AND OVERCORRECTION OF STRABISMUS BY MYOCAMPIMETRY. J. P. JOLY, Arch. d'opht. **7:** 51, 1947.

In this paper, the author describes the use of a myocampimeter in detail, reports 30 cases and comes to some practical conclusions. He states that in cases of convergent strabismus without amblyopia it is necessary to put the eyes in good position by operation and further to help them to acquire binocular vision by stereoscopic exercises. In cases of strabismus with amblyopia the aim should be undercorrection, for at the end of several months or years a progressive divergence is not infrequently encountered. In cases of alternating strabismus an accurate correction is desirable, to be followed with stereoscopic exercises. In divergent strabismus with amblyopia the aim should always be overcorrection. The author has abandoned the older technics and describes a new procedure, which in his hands has proved of great value. He uses tenotomy with a fixation suture. A table of results is presented.

S. B. MARLOW.

Orbit, Eyeball and Accessory Sinuses

THE TREATMENT OF THROMBOSIS OF CAVERNOUS SINUS WITH INTRAARTERIAL INJECTIONS OF PENICILLIN. F. YUSEFOVA and I. NEIMARK, Vestnik oftal. **6:** 52, 1946.

A man aged 24 showed pronounced edema of the lids, chemosis, exophthalmos of 12 to 14 mm. and uveitis of the right eye. A diagnosis

of thrombophlebitis of the orbital veins was made. Intramuscular injections of penicillin were given for several days, with no beneficial results. An orbitotomy combined with opening of the sinuses (after Killian) was performed. There was improvement during the postoperative period of two weeks; then the exophthalmos and chemosis increased again, and the diagnosis of thrombosis of the cavernous sinus was made.

In view of the seriousness of the condition, it was decided to introduce 200,000 units of penicillin into the right common carotid artery, and on the next day the same amount of penicillin was introduced into the left common carotid artery. A few days later the injection of penicillin was repeated into the right carotid artery. The chemosis and exophthalmos were reduced considerably; the vision was increased from counting fingers to 0.1. Three months later the patient showed slight exophthalmos. The intra-arterial injection of penicillin, given as a last resort, most likely saved the life of this patient.

O. SITCHEVSKA.

Pharmacology

ON THE PHARMACOLOGY OF THE BLOOD AQUEOUS BARRIER. A. HUBER, Ophthalmologica **114:** 217 (Oct.-Nov.) 1947.

Using methods which have previously been published (*Ophthalmologica* **111:** 155, 1946), the author has established a normal curve for the appearance into the anterior chamber of fluorescein injected in the blood stream. In this article, he tests quantitatively and qualitatively the effect of certain drugs on the appearance of fluorescein. Pilocarpine and physostigmine increase the permeability of the blood-aqueous barrier to fluorescein. Epinephrine and similar drugs are capable, under certain conditions, of influencing the permeability to fluorescein in the sense of lowering the permeability. Subconjunctival injection of hypertonic solution of sodium chloride causes an intense hyperemia of the ocular vessels and at the same time increases the protein content of the aqueous. In the majority of cases, an increased permeability to fluorescein could also be demonstrated.

F. H. ADLER.

Retina and Optic Nerve

CLINICAL FORMS OF TUBERCULOSIS OF THE MACULA. C. DEJEAN and P. LAPORT, Arch. d'opht. **6:** 397, 1946.

In this article the authors mention four forms of macular retinitis: (1) retinitis with a central white, cotton-like exudate; (2) serous retinitis; (3) brown retinitis, and (4) radiation retinitis. The first two are fairly well known and receive only a brief description. The article deals chiefly with the third and fourth types. In brown macular retinitis the first stage is described as a brick red medallion, and a case illustrating it is presented. The second stage is that of a roughened brown spot, and under this category 3 cases are described. In the third stage nodules are present. Two cases are presented, with drawings in color illustrating some of the transitions which have been observed. In the fourth stage is the black pigmentation in the macula. One case is described. The radiating type of macular retinitis is next discussed, and 2 cases are presented, with drawings in color. The etiologic factor has been consid-

ered to be tuberculous in these cases because of the improvement which has taken place under tuberculin therapy. In none of them was any bacteriologic or serologic evidence available.. Laboratory studies eliminated some of the commoner causes.

S. B. MARLOW.

PSEUDOSTELLATE RETINOPATHY IN A PATIENT WITH A PARAGANGLIOMA. M. APPELMANS, Arch. d'opht. **6**: 448, 1946.

A case of a carpenter aged 30 is described. He had reduction in vision with normal fields and stellate retinitis of the macula with hemorrhages and edema of the disk. The arteries were narrowed, and the reflex was changed. The veins were dilated and tortuous. General examination led to a diagnosis of a tumor of the left adrenal gland. After the extirpation of this tumor notable improvement occurred, with return of vision to ½ in the right eye and to 1 in the left eye. There was a recurrence from metastasis nine years later, but vision remained normal in each eye.

The author presents a description of this lesion and reviews the literature. He points out that this type of lesion may occur in the course of the development of an endocrine tumor having an embryonic sympathetic origin. The symptoms of anxiety, palpitation, tremor, profuse sweating, mydriasis and exophthalmos simulate those of toxic diffuse goiter. The paroxysms of hypertension constitute the sign suggesting an adrenal tumor. The circulatory disturbances, angiospastic in nature, seem to be the primary factor in the retinal lesion. The removal of the tumor resulted in disappearance of the hypertension and the retinal condition. The visual function rapidly improved. The retinal lesions gradually receded.

S. B. MARLOW.

PRESSURE IN THE CENTRAL RETINAL ARTERY. J. I. BARRAQUER MONER, Estud. e inform. oftal. Barcelona, Instituto Barraquer, 1946, no. 9.

The blood pressure in the central retinal artery is measured with the Bailliart opthalmodynamometer, which gives in centimeters of water the pressure necessary to make appear and disappear the pulsation of the central retinal artery. Before one takes the measurement, it is necessary to know the intraocular pressure. The figures so obtained are referred to the Bailliart and Magitot chart, which furnishes in millimeters of mercury the blood pressure in the central retinal artery. Normally the minimum is slightly less than one-half the minimum in the humeral artery and the maximum is slightly above one-half the maximum in the humeral artery. The pressure in the central retinal artery varies with the general blood pressure in keeping with the normal ratio of these pressures. Sometimes the maximum pressure in the central retinal artery is elevated and its normal relation to the maximum pressure in the humeral artery is lost; the former is an indication of the essential systolic pressure in the intracranial vessels. An elevation of the minimum pressure in the central retinal artery allows an early diagnosis of increased intracranial pressure; the pressure in the retinal artery is also elevated in cases of retrobulbar neuritis.

H. ESCAPINI.

DEGENERATIVE DISEASES OF THE MACULA. JONAS DE ARRUDA and S. RAPHAEL SEBAS, Rev. brasil. de oftal. **5:** 3 (March) 1947.

The authors seek to classify the many varieties of degenerative diseases of the macula. They studied the macula under the following aspects: anatomic and histologic, semiologic, pathogenic and nosologic. They have classified thirty-four different types of degenerative diseases of the macula under seven headings: recurrent central retinitis, exudative macular retinitis, cystoid degeneration of the macula, hereditary degeneration of the macula, colloid hereditary degeneration of the macula, macular degeneration of amaurotic familial idiopathy and retinitis exudativa (Coats's retinitis).

M. E. ALVARO.

Trachoma

THE FEDERAL CAMPAIGN AGAINST TRACHOMA. H. CONDE, Rev. brasil. de oftal. **5:** 89 (Dec.) 1946.

The federal campaign against trachoma in Brazil was started in 1943, and since then the ministry of education and health has been making great efforts to eradicate this disease. As in other countries, the immigration into Brazil of infected foreigners (under quarantine nowadays) is considered to have been responsible for the spread of trachoma.

Three foci of endemic trachoma are located inland: in the states of Ceará, São Paulo and Rio Grande do Sul and the regions bordering on these states. Eighty-four units have been organized to combat trachoma, including those of the state of São Paulo, which has been autonomous in this respect since 1904. Epidemiologic inquiries were made in several states, conducted by the sanitary organization, a division of the National Health Department, which supervises the campaign. Model units at Jacarezinho (Paraná) and Crato (Ceará) and a trachoma hospital at Londrina (Paraná), a foreign immigrant center, were inaugurated. Patients with trachoma were given tablets of a sulfonamide drug, with satisfactory results. Owing to the differences in latitudes, the epidemiology of trachoma in Brazil presents certain perculiarities pertaining to each focus. Sanitary engineering has been especially required, with the object of improving the health of field workers (building of public standard bathrooms on coffee farms).

Specialized physicians are trained by an intensive postgraduate course, started in 1943 by the National Health Department. The general plan of this campaign won a prize in the scientific exhibition of the Second Pan-American Congress of Ophthalmology in Montevideo, Uruguay in December 1945.

M. E. ALVARO.

Society Transactions

EDITED BY DR. W. L. BENEDICT

AMERICAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

Frederick C. Cordes, M.D., *Chairman*

Robert J. Masters, M.D., *Secretary*

Ninety-Fifth Annual Session, San Francisco, July 1 to 5, 1946

Chairman's Address: Ophthalmology's Postwar Responsibilities and Opportunities. DR. FREDERICK C. CORDES, San Francisco.

American ophthalmology is faced with the postwar responsibility and opportunity of developing better and more adequate facilities for proper specialty training. An increasingly large number of returning veterans are seeking ophthalmologic teaching; and, since the disruption of European postgraduate teaching facilities, more Central and South American physicians desire training in the United States.

A three or four year residency in a large university medical school is probably the ideal type of training in ophthalmology. The number of these regular residencies, however, is inadequate. For residents in hospitals deficient in instruction in the basic sciences, the basic science course as given by several institutions is recommended. Training can also be obtained through preceptorship, but it is essential that the physician complete the basic course before starting private practice.

For Central and South Americans two types of training facilities should be available: three year residencies in connection with medical schools, and courses that can be given at any time for visiting foreign ophthalmologists. This will bring about a better understanding among ophthalmologists of the Western Hemisphere.

This article was published in full in *The Journal of the American Medical Association* (131:1395 [Aug. 24] 1946).

Industrial Ophthalmology as of 1946. DR. HEDWIG S. KUHN, Hammond, Ind.

It is hoped that through emphasis on a few of the problems in occupational ophthalmology more ophthalmologists will become interested in this field of their specialty. These problems include visual mass testing technics, special corrective procedures, statistical analysis of visual data, coordination between top management and the physician, safety in eyes, illumination and color, minimum industrial eye service and educational opportunities for ophthalmologists and other special personnel interested in industrial work.

This article, with abstract of discussion, was published in full in *The Journal of the American Medical Association* (**132: 772** [Nov. 3] 1946).

ABSTRACT OF DISCUSSION

DR. DERRICK T. VAIL, Chicago: At the moment, the number of ophthalmologists is too small to answer the demands that are made on them. It is planned to train medical technicians, who will be a real aid to ophthalmologists; certainly, industry will be able to use these workers. Optometrists can also be used under the supervision of ophthalmologists, so that this great work of industrial ocular problems can be improved. At present I do not know what is the best approach to the problem of teaching industrial ophthalmology in the medical schools.

DR. A. C. DICK, San Diego, Calif.: Physicians must become more aware of the problems of industrial medicine. New technics in industry have created new physical and mental demands on the worker. Ophthalmologists, like other specialists, contribute most if they look on industry as a community function and apply their special knowledge for the good of the average working citizen.

DR. E. H. CARY, Dallas, Texas: The trouble with present day medical education is that so much information must be given to medical students in thirty-two weeks that the specialties have been pushed aside. I feel that the course in medicine should be extended to about one hundred and seventy-eight weeks before graduation, instead of one hundred and twenty-eight. This would afford the specialists an opportunity to give the student a general training that would be worth while. If the course in ophthalmology can thus be extended, I believe it can supply to industry men who will be far more capable than technicians. I cannot concede that a technician, such as an optometrist, has the knowledge that is essential to aid accurately the people in industry.

Postoperative Complications of Cataract Operation. DR. WILLIAM F. HUGHES JR., and DR. WILLIAM C. OWENS, Baltimore.

This article, with abstract of discussion, was published in full in the November 1947 issue of the ARCHIVES, page 577.

Esotropia Following Occlusion. DR. KENNETH C. SWAN, Portland, Ore.

This article, with abstract of discussion, was published in full in the April 1947 issue of the ARCHIVES, page 444.

Clinical Signs of Diagnostic Importance in Conjunctivitis. DR. PHILLIPS THYGESON, San Jose, Calif.

A number of clinical signs, both gross and microscopic, are of importance in the diagnosis of conjunctivitis. Changes in the regional lymph nodes, the lid margins, the limbus and the cornea are of almost equal diagnostic importance with those occurring in the conjunctiva itself. By such clinical examination it is possible to identify many of

the etiologic types of conjunctivitis. When these clinical observations are correlated with cytologic and bacteriologic studies, the cause can be determined in a high percentage of cases.

Certain clinical findings are individually pathognomonic of a number of etiologic types of conjunctivitis. Thus, the limbal follicles or their cicatricial remains (Herbert's pits) are in themselves unequivocally diagnostic of trachoma. Of similar importance are the chalky concretions (Trantas' spots) in the limbal excrescences of vernal conjunctivitis, and the pavement-block-like papillae on the conjunctiva of the upper tarsus in palpebral vernal conjunctivitis.

Most conjunctival changes, however, are not individually pathognomonic, but are only suggestive of certain etiologic types. Examples of such nonpathognomonic changes include punctate staining of the corneal epithelium, the conjunctival follicle and extension of limbal vessels into the cornea. When several such changes occur simultaneously, however, they may together point to a specific cause. Thus the extension of limbal vessels, when combined with punctate staining of the corneal epithelium, subepithelial infiltrates in the cornea and the follicles on the upper tarsus, gives a composite picture diagnostic of trachoma.

In the same way, punctate staining of the corneal epithelium, in itself not pathognomonic, is clearly indicative of staphylococcic infection when combined with chronic conjunctival inflammation and lesions of the lid margins.

This article was published in full, with abstract of discussion, in *The Journal of the American Medical Association* (**133**: 437 [Feb. 15] 1947).

ABSTRACT OF DISCUSSION

DR. JAMES H. ALLEN, Iowa City: Dr. Thygeson has provided a logical and practical basis for beginning the differential diagnosis of inflammatory and infectious diseases of the eye. Under Dr. Thygeson's influence, my colleagues and I have used this method not only for diagnosis but also for teaching our residents. We find that it is highly stimulating to the residents and that it simplifies teaching. It is unfortunate that time did not permit Dr. Thygeson to extend the differential diagnosis which he uses to its logical completion. The beginning is the differentiation on the basis of a single manifestation—preauricular adenopathy, for instance. The extension, then, is the division into and differentiation of such forms of conjunctivitis as the follicular, nodular and ulcerative.

DR. TRYGVE GUNDERSEN, Boston: Conjunctivitis alone gives rise to few symptoms except those associated with swelling of the conjunctiva, interference with lacrimal drainage and increased secretion of mucus, pus and tears. These, in order, cause a sense of fulness around the eyes, some tearing and, lastly, agglutination of the lids, especially on awakening. When the cornea becomes involved, new symptoms appear. Punctate keratitis, such as that caused by staphylococcus toxin, causes pain—occasionally a definite, deep-seated ache in the globe. Since it is not uncommon for the superficial punctate lesions to heal during the day, with the natural cleansing of the conjunctiva and the washing away of the bacterial toxins, the symptoms also disappear. Therefore, a symptom of diagnostic importance is ocular pain, severest in the early morning and lessening during the day. In contrast to

ocular pain, which is severest on arising and less severe as the day goes on, there are painful sensations which behave in a reverse manner. For instance, in keratoconjunctivitis sicca the healing of the corneal defects occurs during the night, when the lids are closed and the cornea is kept normally moist and lubricated. Therefore the painful sensations of heat and dryness, of which these patients complain, increase during the day. This is particularly true on hot, dry and windy days. Itching is a symptom which is most helpful for the ophthalmologist to elicit, and its presence should never be overlooked when mentioned spontaneously by the patient. To me, it invariably and exclusively indicates allergy. The victim of hay fever knows this. No patient with active vernal conjunctivitis fails to give itching as his most troublesome complaint. It exists even in conjunctivitis due to the prolonged use of atropine, and less frequently that of physostigmine salicylate and pilocarpine. The cause of the itching has never been clearly defined, but I believe that it may be due to, or at least is always associated with, the corneal stippling which Dr. Thygeson has described as fine punctate staining. This change in the cornea is an important type to recognize as an entity. Not all the stippled points do stain with fluorescein sodium. At the Massachusetts Eye and Ear Infirmary we have accepted Vogt's term, "keratitis epithelialis disseminata," and, until a better term is offered, I suggest that this descriptive one be used. The stippling is common; it always exists on the corneas of patients who have active vernal conjunctivitis and frequently on the corneas of patients with other allergic conditions of the eyes. I offer it as possibly the direct cause of ocular itching.

DR. I. S. TASSMAN, Philadelphia: The oculoglandular syndrome of Parinaud was referred to as leptotrichosis, which is what it has been understood to be. I wonder whether Dr. Thygeson could add anything to clarify the relation of the virus of lymphogranuloma venereum to the causation of Parinaud's oculoglandular syndrome.

DR. PHILLIPS THYGESON, San Jose, Calif.: I was particularly interested in having Dr. Gundersen discuss the diagnostic value of the various subjective symptoms of conjunctivitis. Dr. Allen brought out the important relations of the various signs and symptoms of conjunctivitus and showed that, whereas one sign alone may not be diagnostic, the combination of two or more signs may be so. This is well brought out in the case of oculoglandular conjunctivitis, in which the presence of a visibly swollen preauricular node is not in itself diagnostic but when combined with small areas of necrosis in the conjunctiva immediately points to the etiologic entity of leptotrichosis conjunctivae (Verhoeff). There seem to be two schools of thought regarding the oculoglandular syndrome of Parinaud. Dr. Verhoeff, I believe, is of the opinion that there is only one type of Parinaud's conjunctivitis, which is leptotrichosis conjunctivae, of which he discovered the causal agent. The late Dr. Sanford Gifford strongly urged the use of the term "oculoglandular syndrome of Parinaud" to include all the various etiologic types of conjunctivitis characterized by the occurrence of large, swollen preauricular glands. In this syndrome would be included such etiologic entities as tuberculosis of the conjunctiva, conjunctivitis associated with lymphogranuloma venereum and syphilis of the conjunctiva. Ten or more entities would be included in this group. I personally prefer

the term "oculoglandular syndrome of Parinaud" for use in describing a conjunctivitis of this type, at least until the causative agent has been determined, which in many cases will be difficult or impossible.

Goniotomy for Congenital Glaucoma: Urgent Need for Early Diagnosis and Operation. Dr. Otto Barkan, San Francisco..

This article was published in full, with abstract of discussion, in *The Journal of the American Medical Association* (**133:** 526 [Feb. 22] 1947).

ABSTRACT OF DISCUSSION

Dr. Meyer Wiener, Coronado, Calif.: Dr. Barkan's method of incising the trabeculae so as to permit a flow of aqueous into Schlemm's canal gives the best promise of favorable results in treatment of congenital glaucoma. This is especially true if one is able to operate in the early stages, before complete closure of the canal takes place. Dr. Barkan lays particular stress on corneal cloudiness as a clue to the early diagnosis of congenital glaucoma. This must not be confused with rupture of Descemet's membrane due to pressure on the globe during delivery. In this case, however, the cloudiness would not disappear during the day, as it does in the cases of glaucoma. I wonder whether Dr. Barkan has ever used two small, bent hair pins to separate the lids, instead of the ordinary lid retractors; the hair pins give a great deal more room, and I found them more satisfactory. An objection to the use of deep anesthesia in measuring the tension in infants is that the eyes diverge and rotate up, so that one cannot place the tonometer in the exact center of the cornea, as is essential for exact readings, I see no more objection to the local instillation of an anesthetic in the infant, combined with first stage anesthesia, than there would be in the adult. I question the statement that amblyopia is due to nonuse alone. I have seen a case in which the operation was performed forty years after the development of the cataract, with resulting 20/20 vision. I have never seen a true glaucomatous, undermined cup disappear in any circumstances, and it is hard for me to conceive how it can occur, although I should hesitate to question Dr. Barkan's statement to this effect. I am glad that he makes the distinction between goniotomy in the infant, which consists in removing the occluding fetal membrane from the angle, and goniotrabeculotomy in the adult, the object of which is to incise the angle wall—that is, the trabecular body itself. This would also answer the question put by Dr. Allen as to whether the operation should be called goniotomy or trabeculotomy. The results obtained by Dr. Barkan in his operations for congenital glaucoma are so far beyond those of any method heretofore used that one can safely predict that his method will be universally adopted for this type of glaucoma, which, in my experience, gave less promise with the methods before available than any other type of glaucoma. For the purpose of handling cases of congenital glaucoma alone, Dr. Barkan has made one of the important contributions to ophthalmic surgery in modern times.

Dr. Dohrmann K. Pischel, San Francisco: Dr. Barkan gives us information on 88 eyes in 51 patients, all observed by him. Of these, he operated on 76 personally. In 36 of the cured eyes the tension has been normalized for over four years. While the time is too short

to be certain that a final answer has been provided to this difficult problem of hydrophthalmia, Dr. Barkan's results should make us all hopeful that we are at last on the track of the correct solution. The general opinion is that the prognosis in this disease is poor. More or less complete blindness in the affected eyes has been the usual fate. Therefore, good results in a large series of cases should give us hope that patients with congenital glaucoma can be helped if treated properly. There has been a general misunderstanding as to how goniotomy is performed at present. It was first thought that an incision was made in the angle, a direct opening being made into Schlemm's canal. This is not the case. In these hydrophthalmic patients there is an embryonic rest of spongy tissue in the angle which prevents the aqueous from reaching and filtering through the trabecular area. This operation aims at stripping off or wiping off enough of this tissue to open this angle sufficiently to allow normal filtration. The two main points of the paper bear emphasis, the importance of early diagnosis and of early operation. Patients operated on in the first year of life seem to do best. I have had the opportunity of seeing several of the patients with whom Dr. Barkan has been successful, each with a good, clear cornea.

Dr. Thomas D. Allen, Chicago: Dr. Barkan has performed a service in describing the early signs and symptoms of infantile glaucoma, and especially in emphasizing the necessity of determining the intraocular tension with the patient under deep general anesthesia. Several years ago my colleagues and I were having difficulty in comparing the tensions of the patients in one room and the tensions of patients in another. One of the assistants lay down on a bench; I took his tension, and then asked him to squeeze his eye. Meanwhile, I held his lids open carefully, so that there was no pressure on his eye; the tension immediately went up over 20 points, from a normal reading to about 40 mm. If this happens in adults, how much more likely is it to happen in a baby? All are familiar with the stage of excitement during the induction of general anesthesia. If the gross muscles of the body are in a state of spasm, one cannot be sure that the ocular and orbital muscles are relaxed. Deep anesthesia is necessary for intraocular tonometry in babies. I have occasionally attempted the same operative procedure, but I have not had nearly so many cases as has Dr. Barkan. My first difficulty came with the first patient on whom I attempted the operation —a blind girl with numerous elongated peripheral anterior synechias, which I cut. Much bleeding followed from the capillaries in some of the synechias. I should never have attempted the operation in such a case. My greatest objection to this surgical procedure is that several operations are often necesary. Sometimes several are necessary in other types of surgery, too; but usually when other decompressions are attempted, one operation suffices. I agree that the operation is seldom effective after the eyeball has been enlarged for some time. That one so seldom sees and recognizes the situation before enlargement has taken place may be the reason that we have not had as great success as has Dr. Barkan. One should not attempt goniotomy without careful gonioscopic examination. Only by careful study of our cases can we select the proper treatment. With careful operative technic, I feel sure that the average skilled surgeon will find this operation a great help in the prevention of blindness.

DR. EDWARD B. SHAW, San Francisco: Congenital glaucoma is infrequent, but we are grateful to Dr. Barkan for having educated us on the importance of this subject. We were formerly content to feel that this was an abnormality seldom seen and that, if it was encountered, there was so little to do about it that the pediatrician need not be much concerned. Dr. Barkan's work has called to our attention the diagnostic features of the abnormality and has impressed on us the importance of prompt and adequate therapy. I suppose that in the past most of these patients have eventually come under the care of a good ophthalmologist; but I am fearful that many of them have been temporized with too long with the idea of their having either an infectious or a metabolic disturbance and that a considerable and regrettable loss of time has occurred. Now that we have learned to recognize the importance of this emergency and the proper operative care, I have been particularly impressed with the success of the end results. There is in all pediatrics no more delightful result than to see good vision after operation in such a patient, who had the prospect neither of seeing nor of looking well.

DR. PETER C. KRONFELD, Chicago: I should like to put myself on record as a recent convert to the idea of goniotomy as the specific operation for the type of congenital glaucoma in which a layer of embryonic tissue covers the anterior wall of the angle. This layer of embryonic tissue may escape attention, but in most cases of congenital glaucoma such a layer is present. Again, we must ask ourselves the question: Is "goniotomy" the proper term for this operation? As it is practiced now, it is a stripping of the trabecular area without any actual incision. It would be helpful if Dr. Barkan would describe the operation in exactly the way in which he now does it. It is clear to me that goniotomy as it is practiced now gives much better results than iridencleisis. There are successes with iridencleisis, but the frequency of those successes is much lower than that in Dr. Barkan's series. I should like also to apologize to my colleague from Chicago, Dr. Allen, whose paper before the meeting of the American Ophthalmological Society in 1944 I had the pleasure of discussing. At that time Dr. Allen presented a case of hydrophthalmos in which he had performed goniotomies, with successful results. The gonioscopic picture in that case resembled the picture after a cyclodialysis; and in my discussion I erroneously arrived at the conclusion that Dr. Allen had cured that patient with a cyclodialysis which he had done by a rather devious route. I now believe that the principle of that operation was the principle of goniotomy, namely, the stripping of the trabecular area. A dissecting spatula introduced into the anterior chamber at an angle from the front will accomplish such a stripping more easily and extensively than a dissecting spatula introduced from behind. Goniotomy represents a definite progress in the treatment of hydrophthalmos.

DR. OTTO BARKAN, San Francisco: Dr. Wiener's suggestion of the use of hair pins appeals to me as a good one. Disappearance of a cup after normalization of pressure is mentioned in Anderson's book (Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939, p. 104). There was 1 case of this occurrence in

my series. I use the contact glass if the cornea is transparent. It is a great comfort in cases of monocular patients to operate with the contact glass and to be assured that a hemorrhage will not occur. All patients with a transparent cornea reacted excellently to the operation performed with the glass and did not require repetition. I have tried air as an aid to goniotomy, but in the adult the loss of magnification is a handicap. How it will turn out in operations for congenital glaucoma remains to be seen. I am obliged to Dr. Pischel for calling attention to the stripping of the angle and to Dr. Allen for his remarks on the technic of goniotomy. Dr. Kronfeld raised the question of the name of the operation, "goniotomy." It is true that it is not an incision. In the first cases I did incise, but there are definite handicaps if one gets an adhesion of the root of the iris to the area of incision in the angle wall. I now use a rather dull-pointed knife, with the intention not of making a counterpuncture, but merely of stripping the embryonic tissue from the angle wall. In none of these cases have I seen an internal cyclodialysis, except possibly in 1 case. In adults it is true that the reduction of pressure following goniotrabeculotomy may be the result of an internal cyclodialysis. That is not the purpose of the operation, however; the intention in operation on adults is actually to incise the trabecular body. With infants the intention is to strip the angle of fetal tissue. I should like also to thank Dr. Shaw for calling attention to the pediatrician's point of view, which is important because so many infants with this condition are first seen by the pediatrician, and he should be aware of the possibility of glaucoma.

A Neglected Cause of Secondary Glaucoma in Eyes in Which the Lens Is Absent or Subluxated. Dr. Paul A. Chandler and Dr. Carl C. Johnson, Boston.

This article, with abstract of discussion, was published in full in the June 1947 issue of the Archives, page 740.

Inheritance of Retinoblastoma: Two Families Supplying Evidence. Dr. Harold F. Falls, Ann Arbor, Mich.

A new pedigree is presented with evidence of bilateral retinoblastoma in female identical twins, the disease appearing at approximately 6 months of age in both. In the absence of surgical or roentgen therapy, fairly rapid intracranial extension of the tumor led to the death of both children. This is the third reported instance of retinoblastoma in identical twins.

A second new pedigree presents another family in which both the horizontal and the vertical occurrence of retinoblastoma was observed.

Retinoblastoma may have different genotypes, and it is not necessary to interpret all pedigrees in terms of a single mechanism of inheritance.

Parents who have produced a child with retinoblastoma should be urged to discontinue having children, and children surviving enucleation for retinoblastoma should be sterilized.

This article was published in full, with abstract of discussion, in *The Journal of the American Medical Association* (**133:** 171 [Jan. 18] 1947).

ABSTRACT OF DISCUSSION

DR. A. B. REESE, New York: I should like to cite 2 tragic instances illustrating the practical importance of what Dr. Falls has said. A father who in infancy had had both eyes enucleated because of retinoblastoma was not told of the danger of reproducing the disease, and his only child had bilateral retinoblastoma and bilateral enucleation. The child is still living, after several years.

A father who had bilateral retinoblastoma and bilateral enucleation in infancy was advised after marriage that it would be safe to have children. The first child had bilateral retinoblastoma and bilateral enucleation and survives. Before the fate of the first child was known, a second child was conceived. This child also has bilateral retinoblastoma, for which an enucleation has been done on the eye with the more advanced growth. The fellow eye is being treated with radiation.

DR. C. WILBUR RUCKER, Rochester, Minn.: In the light of present knowledge, Dr. Falls is certainly correct in urging that parents who have produced a child with retinoblastoma discontinue having children and that persons who survive enucleation for retinoblastoma remain childless. With respect to the latter, however, he is taking a hazardous step when he advocates sterilization during childhood. Society would benefit by it, without a doubt, but the physician who performs a sterilizing operation on a child, in the absence of a specific statute to the contrary, makes himself liable to a suit for assault, instituted by the patient when he reaches the age of 21 years. It is my opinion that the physician should not risk the possibility of a ruinous legal suit, even for his convictions about eugenics, and that he had better content himself with giving advice on the use of contraceptives.

DR. HAROLD F. FALLS, Ann Arbor, Mich.: Lesions resembling retinoblastoma have been produced by synthetic substances. In this respect, it is important to state that the genes are complex chemicals, and thus effect mutant changes, possibly in a manner similar to that of noxious agents. It is impossible for the clinician to determine, in many isolated cases, whether the anomaly in question is the effect of a genetic influence or that of a noxious chemical or physical factor. Dr. Rucker has suggested that it is legally dangerous to advise sterilization of minors. I agree, but for the benefit of the race, and also to prevent the misery, the pain and the discomfort to both the parents and the affected offspring, I strongly advocate sterilization. We as physicians can only advise; the initiative falls on the parents.

Practice of Neurology in the United States. DR. PERCIVAL BAILEY, Chicago.

The author analyzes and discusses the relation of psychiatry and diagnostic neurology and that of neurosurgery and diagnostic neurology. He asserts that pure clinical neurology has reached an all time low in this country. He concludes that neurology should strengthen its ties with neurosurgery and should divorce itself from psychiatry.

Present Trends in the Practice of Neurology. Dr. George Wilson and Dr. Charles Rupp Jr., Philadelphia.

From many quarters, there arise divers voices intimating that in this day and time the clinical neurologist is destined to become merely an anachronism. Chief among those anticipating the early demise of the clinical neurologist is his colleague, the psychiatrist. Originally motivated by the intention of stressing the interdependence of body and psyche, it appears that, with a few exceptions, most of the psychosomaticists have become too preoccupied with the aspects of the psyche, to the neglect of the soma. Regardless of whether the cause of the so-called functional psychoses ultimately proves to be neuronogenically or psychogenically determined, the psychiatrist can no more hope to comprehend the problems of his present day patients if he is devoid of any knowledge of clinical neurology than can the neurologist attempt to treat even the simplest form of paralysis without some knowledge of the structure and functions of the personality. If the neurologist can acquire a respectable mastery of the fundamentals of psychiatry, is it beyond the capability of the psychiatrist to possess an equivalent knowledge of the basic anatomy, physiology, pathology and clinical disturbances of the nervous system?

In the warfare against the ravages of disease of the nervous system, there is no place for internecine strife and bickering as to what is purely neurologic and what is purely psychiatric, or purely neurosurgical. Future progress requires the coordinated teamwork of the clinical neurologist, the psychiatrist, the internist and the neurosurgeon, mutually strengthened by the assistance of the neuroanatomist, the neurophysiologist, the neuropathologist, the biochemist and workers in the other basic medical sciences.

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ABSTRACT OF DISCUSSION

Dr. J. M. Nielsen, Los Angeles: I wish to point out that clinical neurology is only staggering a little; it is not going down. Let us see what has happened in psychiatry in the last few decades. Every advance in psychiatry that has been made in the last few decades has been made on the basis of the concept that the mind resides in the brain. Insulin shock replaced the former psychotherapy of dementia precox. Metrazol® shock, and then electric shock, came along, and have even surpassed insulin shock in therapeutic results. These methods of therapy do not shock the patient into a willingness to get well; they make him well in spite of himself by correcting to a large extent the abnormal condition that exists in the brain. The brain is the organ of the mind. Every thought, every idea of any sort, every hallucination, every delusion, has a neural basis. There cannot be a thought without its traveling over the neurons of the brain.

There are many things which we neurologists do not know. We do not have any idea, or misconception, that there is a certain focus in the brain a lesion in which will produce a psychoneurosis. We believe that a psychoneurosis results from a poor use of normal structure. We do

not want to pretend to know anything which we do not know; we wish only to extend gradually, perhaps slowly. But we believe that within another half-century psychiatry will be well understood on the basis of neurology.

With regard to the neurosurgeon and clinical neurology, there is a certain temperamental difference between a surgeon and a clinical neurologist. A surgeon wants action, and he wants it in a hurry. He wants to remove that lesion and have the patient well. He is not much of a philosopher as a rule. The neurologist has the philosophic attitude of the psychiatrist and the technical leaning of a neurosurgeon, and that is where he comes in. He is willing to spend months, if necessary, in studying and restudying the case and in deciding whether surgical intervention is needed. I think that there will be a constant, good liaison between the neurosurgeon and the neurologist simply because they are necessary to each other.

DR. JOHN B. DOYLE, Los Angeles: It is greatly to the credit of Dr. Wilson and Dr. Rupp that they have brought into the open the discussion of a problem of such fundamental importance. Society at large, and the medical profession in particular, has for several generations been threatened by the development of a dichotomy between those interested in the total expression of the nervous system of man and lower animals and those interested solely in psychiatric norms and deviations. The problem has been complicated during the twentieth century by the evolution of neurosurgery and, to a lesser degree, by the changing purviews of the internist, the pediatrician, the syphilologist and the allergist. In my opinion, the situation which confronts those of us who are interested in the nervous system as a whole, in the advancement of knowledge and in the elevation of standards of practice in neurology and psychiatry is not one which should put us on the defensive or lead to acrimonious generalizations or ultimatums. The logical approach to anything like a satisfactory resolution of the evils that have arisen, and the greater ones that hover in the future, is through a program of education of the people as a whole and of administrators of the medical services of the Army, Navy and public health, of hospitals and of medical schools. Such a campaign may at first glance appear grandiose and impractical. Yet it is the means by which the more vocal portion of our specialty has advanced itself to a point where it threatens the extinction of progress in neuroanatomy, neurophysiology, neuropathology and clinical neurology, the sciences from which psychiatry has derived its essential substance.

DR. WALTER F. SCHALLER, San Francisco: I practice neurology by choice, but psychiatry by necessity of keeping busy, because of the inclusion of clinical neurology in so many other specialties and the close relation between neurology and psychiatry. It is apparent from Dr. Rupp's report that the psychiatrist often lacks a sufficient foundation in neurology or has forgotten what he has learned about neurology. Assuming that the latter is true, perhaps the explanation is not too difficult because of the wide field that psychiatry is now attempting to cover. For example, I have had requests to examine patients who wished consultations because of household dissensions, maladjustment in marriage, unrequited love or draft evasion, because they were dissatisfied pensioners or because they wished to evade the penalties of the

law. I often advise these patients to consult their parents, their religious adviser or their lawyer or, as an alternative, to go to a psychoanalyst. Is it, then, any wonder that many psychiatrists cannot keep pace with scientific advances in neurology and psychiatry? I find that "neurology" is defined in Webster's "New International" as "that branch of science which treats of the nervous system." Unless psychiatrists object to this definition, they must admit that their specialty is but a part of neurology. I shall conclude by quoting a paragraph of Dr. Pearce Bailey's paper read before the American Neurological Association last week. It is so conservative and so well worded that I am sure that those of you who heard it will be pleased to hear it again. "I do not believe that the existing predominance of a psychologic orientation constitutes a valid cause for alarm to clinical neurologists. After all, the psychologic approach represents only a particular method or technic for the investigation of the disorganized nervous economy. It cannot presume to rise above the constellation of physiologic and social forces, of which it is a part, any more than water can be expected to rise above its source."

Dr. Roland P. MacKay, Chicago: Lest it be thought that this is merely a session of breast beating on the part of neurologists, I should like to emphasize two points. The neurologist himself is often to blame for the difficult situation in which he finds himself. Many neurologists have so divorced themselves from the knowledge of medicine and surgery in general that they are placed by their confreres in the class of partial physicians. Perhaps that condition arose from the fact that neurologists originally were closely associated with state hospitals and lived in an ivory tower, far from the practice of medicine. A good neurologist is one who knows general medicine, because the majority of symptoms which come under his purview have their origin in general conditions. If the neurologist wants to endear himself to the heart of the internist, he will have to know more about general medicine, and so make his specialty applicable in the mind of the internist. My second point is that the neurologist's difficult situation is in no small part due to the referring physician, sometimes the ophthalmologist. Because of the unpretentious role of medical neurology and the brilliance of neurosurgery since Horsley, because the sunlight of popular attention glitters on the silver scalpel in the surgeon's hands and because neurosurgery deals with organic conditions, the average physician has come to identify organic neurology with neurosurgery and, contrariwise, to identify the neurologist with the functional or psychogenic disorders. It is not necessary to send every patient with a homonymous field defect to a neurosurgeon. Perhaps the majority of patients who have field defects should go to a medical neurologist rather than to a neurosurgeon. It is not necessary to send every patient who limps or has some motor difficulty to a neurosurgeon. In fact, the neurosurgeon, because of his diagnostic limitations and because his attention is directed primarily to surgical conditions, is not able to make a correct and thoroughgoing appraisal of such cases. The fault is the neurologist's in not keeping his mind open to the whole broad field of medicine, and, second, it is the fault of the referring physician, because he identifies

organic conditions with surgical intervention. Both these mistakes can be rectified easily, and perhaps the future of neurology will be much brighter than the Cassandras think.

DR. HENRY R. VIETS, Boston: I should agree that neurology is at a low ebb; but, as I see the subject, the tide is turning, and turning rapidly. Witness the extraordinary enthusiasm of the meeting of the American Neurological Association last week in San Francisco under Dr. Schaller, the establishment of a strong department of neurology in the University of California Medical School under Dr. Aring and the fact that we are discussing this very problem here at the meeting of the American Medical Association. Neurology can be advanced only by neurologists. The minute a department in a medical school, or even in a hospital is abandoned, as has unfortunately occurred in this country, neurology falls to a low level as far as the advancement of knowledge of nervous diseases is concerned. In a medical school, perhaps our primary duty is to train medical students; and we must realize that a sound training in neurology is essential for the practice of general medicine, which, after all, is what 85 per cent of our students are going to do. Osler used to say that 15 to 20 per cent of his diagnostic problems in consultations were neurologic, and 50 per cent of his early papers were written on neurologic subjects. He, like every outstanding internist, was a good neurologist; but the exceptions are many, and the average internist or specialist in other fields of medicine cannot be a good neurologist. Only the neurologist can be a good neurologist, and only the neurologist will advance the knowledge of disease of the nervous system.

Ocular Manifestations of Psychosomatic Disorders. DR. DAVID O. HARRINGTON, San Francisco.

The precision of diagnostic and therapeutic procedure available to ophthalmology has led to a conspicuous neglect of psychic factors in ocular disease. Prolonged, but reversible, physiologic disturbance can eventually give way to irreversible organic disease in the eye, as well as in other body systems. The following ocular manifestations of disturbed psychosomatic relations were described and discussed:

1. Ocular manifestations of vasomotor disturbance
   - (*a*) Amaurosis fugax
   - (*b*) Migraine
   - (*c*) Neurocirculatory asthenia
   - (*d*) Central angiospastic retinopathy
   - (*e*) Raynaud's disease
2. Glaucoma
3. Ocular manifestations of hysteria

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ABSTRACT OF DISCUSSION

DR. GEORGE S. CAMPION, San Francisco: The presenting ocular symptom, as Dr. Harrington has pointed out, was a transitory "black-out" in an unusual number of cases. It occurred in periodic epidemics

when personnel were to be dropped from classes in a technical training school for scholastic reasons. Personnel failing in a training course were shipped out immediately with a rating of seaman, second class, to get some first hand knowledge of the war, so that it was simple to understand the emotional disturbance which preceded the visual symptoms. Occasionally, true migraine would appear in this group, often with the initial attack. The patients with migraine all had good grades up to a certain point and then dropped to the bottom of the class. The threat of failure then precipitated the attack. I saw 1 case of central angiospastic retinopathy in this group. I had first seen the patient three months previously because of bilateral acute contagious conjunctivitis, and I had difficulty getting him out of the hospital. He left quietly after two weeks and then came back with a corneal foreign body, which was removed. I went through the same procedure again, arranging for a gastrointestinal series of tests and a psychiatric consultation. The latter revealed an anxiety neurosis not judged sufficient for a survey with a view to his removal from the service. He reported to duty again after several weeks, and a short time later returned to me with the complaint that his right eye had lost its vision that morning at about 11 a. m. He knew the exact time because he tested his vision twice a day! Examination revealed typical acute central angiospastic retinopathy. He received treatment with all the vasodilators which can be used with safety, including intravenous injections of typhoid vaccine, and had three sessions with the psychiatrist. The edema subsided in four days, which is the shortest time in which I have ever seen this occur, but the macula was permanently damaged. The patient was a radio singer in civilian life, and I firmly believe that the attempt to make an aviation machinist's mate out of him caused him to lose the vision of one eye.

Dr. Meyer A. Zeligs, San Francisco: The role which psychodynamic mechanisms play in vasomotor diseases, such as Raynaud's disease, migraine and retinal angiospasm, has not been clearly appreciated by most practitioners. Dr. Harrington has shown how certain types of ocular disturbances, particularly amaurosis fugax and angiospastic retinopathy, have, in the light of psychodynamic principles, become more clearly understood and nosologically alined. Dr. Harrington has pointed out the dynamic relation between psychic conflict and autonomic instability in patients with these types of ocular disturbance. My own experience in the Navy has borne this out almost exactly. Dr. Harrington and I had been studying these cases among Naval personnel simultaneously in different parts of the world. We later discovered that we had arrived at similar conclusions regarding the role of psychosomatic factors in such cases, particularly in cases of angiospastic retinopathy which had developed in military personnel under the stress of combat. These anxiety or fear states constitute the core about which subsequent psychosomatic reactions characteristically develop. I do not believe that the ophthalmologist can remain content to treat such patients merely by asking them to abstain from smoking or by prescribing an antispasmodic drug to be used when symptoms of retinal spasm occur, or to prescribe such treatment in cases of angiospastic retinopathy after a central scotoma is already demonstrable and unmistakable organic

changes in the retina are visible. Since the psychic disturbances of civilian life are, as a rule, slowly engendered and often date back to early life, persons with ocular disturbances of this type should be given the opportunity of a "preventive" psychotherapy, in which defects of personality or neurotic conflicts are dealt with, even though those psychic disturbances may not, from an ophthalmologic standpoint, seem directly related to the presenting ocular disturbance.

DR. ARTHUR J. BEDELL, Albany, N. Y.: I shall, at Dr. Harrington's suggestion, show you what central angiospastic retinopathy looks like. The slides are photographs of the fundus, showing preretinal edema in its various stages. At the onset there is a dark circle with a brilliant convex surface overlying the macula. As the edema subsides, the circle enlarges until it finally disappears, leaving fine dots of deep pigmentation. This cycle of development was first reported by me in 1928. The cause of the disease is not established. The photographs are shown to supplement Dr. Harrington's excellent paper.

DR. WALTER S. ATKINSON, Watertown, N. Y.: In the discussion of Dr. Harrington's interesting paper, it might be appropriate to report the observation of lenticular opacities in 3 patients after treatment with electric shock. As Dr. Harrington did not have time to present his whole paper, I do not know whether he refers to cases in which treatment with electric shock is used. The lenticular opacities in the patients referred to were mostly subcapsular and in the superficial cortical fibers. The patients were in the second or third decade of life. Two had been examined by me prior to the treatment and no lenticular opacities had been observed. Two have been under observation for over two years, and the opacities have not increased. The third committed suicide before any progress in the opacities was noted. Since no report of lenticular opacities following treatment with electric shock has been found in the literature, it might seem advisable to have an examination of the eyes, with particular attention to the lenses, prior to treatment with electric shock and afterward.

The Surgical Problem of Intracranial Aneurysm and Allied Vascular Lesions. DR. JOHN MARTIN, Chicago.

The author analyzed 52 cases of vascular anomalies of the brain. Of these cases, 17 were of arterial aneurysm, 10 of arteriovenous fistula and 25 of congenital malformations. Except for the relation between trauma and carotid-cavernous fistula, few patients gave reliable hints as to the cause of their disease. The duration of symptoms varied from immediate onset to as long as thirty years.

Roentgenography and cerebral angiography were helpful diagnostic adjuncts in a number of cases. Treatment is difficult and may include craniotomy or ligation of the internal carotid artery.

ABSTRACT OF DISCUSSION

DR. JOHN RAFF, Portland, Ore.: Surgeons have been hesitant about attacking intracranial aneurysms because of two factors, namely, the difficulty of localizing the aneurysm and the hazards attending surgical treatment. Advances within the last ten years have proved helpful both in localization and in surgical treatment. Dandy's monograph,

published two years ago, helped to clarify the localization of aneurysms from clinical signs. However, for the localization of small leaking aneurysms, methods other than clinical signs must be used, and cerebral arteriography seems the most promising. Hemorrhage from leaking aneurysms is so often ultimately fatal that, even though technically difficult, arteriography must come into greater use. I have had little success in injecting a colloidal suspension of thorium dioxide into the carotid artery without exposing the vessel in the neck. Others report that they have mastered the closed technic. Once an aneurysm has been localized by clinical methods or by arteriograms, the question arises whether the involved vessel can be safely ligated. The Matas test may answer the question. I have never been convinced that digital compression of the common carotid artery once or twice a day for two weeks will stimulate the production of an adequate collateral circulation in patients who will not tolerate ligation of the internal carotid artery. I always perform all ligations of the internal carotid artery with the use of local anesthesia and compress the internal carotid artery for at least thirty minutes before final ligation. However, even though no untoward symptoms develop for thirty minutes, the surgeon's worries are not over. An illustration is the case of a woman aged 39 seen about one year ago with the typical signs of an aneurysm of the right internal carotid artery. The internal carotid artery was ligated with heavy silk over preserved fascia, the latter being used to prevent injury to the intima. She tolerated the ligation well for twenty-four hours; then hemiparesis developed. Now, a year later, she still has slight spasticity of the left side, but the proptosis of the right eye and the ophthalmoplegia have disappeared. In my experience, congenital angiomatous malformations are frequently accompanied with epilepsy. I have on occasion operated on such patients and attempted to remove or obliterate the vessels but have had little success in decreasing the frequency of the seizures. Pilcher reported that 2 of his 3 patients treated by radical operation were relieved of epilepsy.

Dr. Hale A. Haven, Seattle: I was especially interested in Dr. Martin's observation that headache was a common and major symptom in patients with aneurysm. I note that he qualified that statement by saying, "among whom there was a high incidence of intracranial bleeding." I wonder how often, in his experience, such headaches occurred in cases of discrete aneurysm in which, as far as he could determine, there had not been bleeding, and how often the headaches had occurred prior to the occurrence of the intracranial bleeding. Several years ago Dr. B. T. Horton, of the Mayo Clinic, pointed out that in many cases of hemicrania or migraine-like headaches a relatively discrete aneurysm, frequently intracerebral, was thought to be a causative factor in the headache. All too often one first sees the patient after he or she has had a disabling, severe, or even fatal, hemorrhage from a lesion of this kind. Is there anything in the symptoms or findings in Dr. Martin's cases which would lead one to an earlier diagnosis or a logical treatment for such lesions, aside, perhaps, from one's daring to make an earlier angiographic study in cases in which there is a remote suspicion? I am well aware that for years there has been much controversy

over the question of preliminary compression before ligation of the carotid artery. Personally, since an unhappy experience several years ago, in which the patient died with massive softening of almost the entire left hemisphere after ligation of the internal carotid artery, preceded by preliminary digital compression, I have used a collar type of compressor, similar to the one devised by Keegan, and for a gradually increasing time. Since I have followed this practice I have had no untoward results. I should like to call attention to the preliminary control of both carotid arteries, as advocated by Hamby, in attacking the intracranial vascular lesions.

Dr. Cullen Ward Irish, Los Angeles: In a rather extensive study of vascular encephalopathy, accomplished several years ago, there was included a briefer survey of aneurysms found in 1,000 cases of cerebral vascular accidents observed at 12,503 necropsies. In this group, 40 cerebral aneurysms were demonstrated in 32 cases. Aneurysmal rupture appeared in 20 of the 32 cases, and the aneurysmal dilatation remained unruptured an equal number of times. Twenty-nine of the 40 aneurysms were present in 25 cases of cerebral hemorrhages, which had resulted from ruptured aneurysm in 20 cases and from other vascular ruptures in 5. Five aneurysmal dilatations appeared in 3 brains in which thrombotic processes had occurred, and 6 aneurysms were found in 4 brains in which neither hemorrhagic nor thrombotic lesions were present. The sites of the 40 aneurysmal lesions in this series were as follows: Fifteen were in the middle cerebral artery, with 5 ruptured; 8 in the anterior cerebral artery, with 6 ruptured; 7 in the basilar artery, with 4 ruptured; 5 in the vertebral arteries, with 1 ruptured on each side; 3 in the left internal carotid artery, with but 1 ruptured, and 2 in the anterior communicating arteries, with both ruptured. Twenty of the lesions were on the left side and 11 on the right side, and 9 were nonlateralized, with involvement of the anterior communicating and basilar arteries. The carotid system was involved in 28 cases and the basilar system in 12 cases. The causal factors in the production of the aneurysms in the 32 patients appeared to be: congenital developmental anomalies in 10; emboli, in 4; arteriosclerotic disease, in 13; atheromatous lesions, in 1, and syphilis with resulting arteriosclerotic processes, in 2. The ages of these 32 patients varied from 27 to 81, with an average of 52.4 years. Fifteen were men and 17 were women. For but 6 there were reports of premonitory symptoms of the presence of an aneurysm. I would bespeak more conscious thought in all cerebral vascular conditions with regard to the possible presence of aneurysms. The incidence, of course, is not high, but with the increasing technical ability of our neurosurgeons, many of these aneurysms can be attacked and lives saved.

Dr. Arthur J. Bedell, Albany, N. Y.: Four colored photographs in 2 cases were presented. The first case was that of a woman aged 52 who reported six days after a cloud came before her right eye. Vision was 1/200; the pupil was 3 mm. in diameter and was regular and active; the media were clear; the disk was swollen 3 D., with several fine, superficial retinal hemorrhages, and the veins were overfull. The field of vision showed pronounced contraction, with a large, oval central scotoma. The diagnosis of aneurysm was made by Dr. Horrax. After

roentgen ray treatments the patient showed great improvement. In her subsequent photograph the right disk was pale and sharply and clearly outlined. Both the arteries and the veins were smaller than normal. Vision was improved to 20/30. In contrast to this case is a case of traumatic arteriovenous aneurysm on the right side, terminating in pulsating exophthalmos. The fundus pictures were unusual, and for that reason the photographs were shown. In the right eye the retinal veins and arteries were almost equal in size and color. The entire fundus was pink. The differentiation between the disk and the surrounding retina was slight, so that the appearance was that of a small optic nerve head. In the left eye the disk was not so small as in the right; there was less congestion, and the margins of the papilla were more distinct. Both nerves returned to their normal size after ligation of the right common carotid artery. The demonstration of photographs of the fundus at the time of the presentation of clinical cases adds much to the accuracy of observation; and for that reason these 2 cases were presented in conjunction with Dr. Martin's discussion.

DR. JOHN MARTIN, Chicago: I agree with Dr. Raaf that epilepsy is one of the major clinical signs in cases of congenital vascular anomalies of the brain. We at Northwestern University have not had the success in the treatment of these anomalous lesions that Dr. Pilcher described at the recent meeting of the neurosurgeons in Nashville, Tenn. I wish we could have such good results. I agree that to call them angiomatous malformations, or some such simple inclusive term, is logical in everyday parlance and is convenient. I have been somewhat confused by the Latin names, which obviously mean different things to different authors, and that is why I have reduced them to the simplest terms in describing their pathologic anatomy. In answer to Dr. Haven: of the 17 patients with aneurysm, 16 had headaches as a major symptom. Eight patients had definite clinical signs of intracranial bleeding. We have also felt that the advantage of compression of the carotid artery lay in making us feel better before the operation rather than in doing the patient good. We have, however, used the collar compressor, with what we believe to be effectivenes. Angiography is convenient and helpful, but one may be thwarted in attempts to make such an examination, as shown by a recent case of mine, that of a sailor, 21 years old, who suddenly, on minor exertion, had a severe bout of intracranial bleeding. The hemorrhage cleared up, leaving him a little "fuzzy," and recurred in a month. Within the next month it recurred three times. At no time until just before his death were we able to lateralize the lesion. At least, we thought that we had lateralized it. He was never in condition after the second episode of bleeding for even ligation of the carotid artery, if we had decided to do such a thing or could have lateralized the lesion. Autopsy revealed a tremendous aneurysm which obviously had been bleeding a great deal, as we know, before death. I do not know whether angiography would have revealed that lesion or not, for the actual circulating content of the aneurysm was small and the surrounding necrotic clot was rather large. I am thankful to Dr. Irish for his comments on the causation of aneurysm. That, to me, was the most interest-

ing part of his subject. Dr. Bedell's excellent pictures have shown the fundus better than most of us see it through the ophthalmoscope.

Changes in the Visual Fields Confirmed by Pathologic Diagnosis.
DR. DONALD J. LYLE, Cincinnati.

An important aid to the diagnosis of intracranial lesions is a careful study of the visual fields. Defects in the visual fields vary according to the location and type of lesion. The chief components of the visual system are the retrobulbar optic nerve, the optic chiasm, the optic tract, the optic radiations and the visual cortex. The types of lesions are loosely grouped into inflammations, tumors and vascular disorders. When defects in the visual fields are found, they may aid in determining the location and the nature of a lesion and its activity and prognosis.

This article was published in full, with abstract of discussion, in *The Journal of the American Medical Association* (**133**: 517 [Feb. 22] 1947).

ABSTRACT OF DISCUSSION

DR. JOHN S. MCGAVIC, Phoenixville, Pa.: Both the ophthalmologist and the neurologist may profit from a study in which clinical observations are confirmed by pathologic specimens, such as Dr. Lyle has just presented. I wish that Dr. Lyle would give us his opinion about sparing of the fixation area in patients with hemianopsia. An important factor brought out by Dr. Lyle bears reemphasis. The areas of perception, recognition and interpretation (areas 17, 18 and 19 of Brodmann) are separately represented in the visual cortex, although they are integrated by intragyral and intergyral fibers. One may, therefore, be misled in interpreting defects in the fields because the patient may see and not recognize, or may see and recognize but fail to interpret the image to the examiner, and so forth. Lesions in the angular and supramarginal gyri, in the posterior portion of the parietal lobe, produce symptoms bizarre to the patient and lead to confusion on the part of both patient and examiner. In other words, the psychic visual area may be involved alone or in addition to the receptive portion of the calcarine area. One must always keep in mind that the determination of the visual fields is a subjective examination. Repetition of studies of the fields is therefore extremely important in order that accuracy may be insured, as well as changes in the defects followed, in the diagnosis of ocular and neurologic disorders. After the liberation of American soldiers from the Japanese prison camps, one began to see many patients with nutritional amblyopia. The majority of these patients had normal peripheral fields with relative or absolute central or paracentral scotoma. The size and shape of the central and cecocentral scotomas varied tremendously, but practically all had cecocentral scotomas for red test objects. Despite all arguments for quantitative determination of fields with various sizes of white test objects, there can be no doubt that with these patients it was far easier and more satisfactory to elicit a defect when red test objects were used. Many patients with considerable reduction in visual acuity and with definite central scotomas showed nerve heads which were well within normal limits. These patients had learned to use their eyes to the best advantage—fixing just to one side

of the object and shifting fixation rapidly to build a picture from several partial images. None of them complained about anything—all felt that their vision was better than it actually was. I should like to emphasize what Dr. Lyle has said, that is, that the ophthalmologist's contribution to diagnosis would be greater if he saw the patient earlier. It is regrettable that there has not been more teamwork and exchanging of information between the ophthalmologist and the neurologist. It is my feeling that this teamwork should start between the residents in the neurologic and ophthalmologic services of the hospitals and should continue as they become attending staff members.

DR. P. J. LEINFELDER, Iowa City: At times, pathologic processes cause seemingly incredible symptoms. Bitemporal or homonymous hemianopsia may be caused by a dilated third ventricle, the result of a shift of the anterior part of the ventricular system and of a kinking in the aqueduct of Sylvius. In producing homonymous hemianopsia, a frontoparietal tumor may act in two ways. The pressure may be on the ipsilateral tract by herniated brain substance in the region of the uncinate gyrus, or it may be contralateral, due to transferred pressure, squeezing the tract between the brain stem and the compressed temporal lobe. Lesions of the internal capsule cause a homonymous hemianopsia with hemianesthesia, but only rarely is the lesion large enough to cause concomitant hemiplegia; if hemiplegia accompanies such a lesion, the coma precludes diagnosis of the visual loss. Hemiplegia and homonymous hemianopsia are the result of a lesion on the basal surface of the brain in the region where the optic tract swings around the cerebral peduncles and the contained pyramidal tracts. Tumor of the pituitary gland may exist without resulting in changes in the fields or without roentgenologic evidence of destruction of the sella. In an occasional case the syndrome of cerebral tumor is fully developed, with choked disks and increased intracranial pressure, but without localizing signs. Careful examination by all methods known to the neurosurgeon may fail to disclose a neoplasm or any reason for the increased intracranial pressure. In such cases operation reveals turgescence of the brain, which is transient but recurrent. This syndrome has been named "pseudotumor." Some relief has been gained by trephination, but the choked disk may persist for months and years. I have observed such a case for more than four years, during which time the elevation of the nerve head has been present at each examination but the visual fields have remained normal. Textbooks state that temporal pallor is a pathognomonic sign of multiple sclerosis. Temporal pallor is a common physiologic finding and is of no diagnostic importance in cases of multiple sclerosis unless it is accompanied with diminished central visual acuity; this means, then, that a preexisting retrobulbar neuritis has destroyed some of the visual fibers and produced real optic nerve atrophy and a central scotoma.

DR. DONALD J. LYLE, Cincinnati: I wish to thank Dr. McGavic and Dr. Leinfelder for their discussions. Dr. McGavic asked me why the fixation area is spared in patients with hemianopsia. Several reasons have been advanced for sparing of the macula: (1) a crossing of macular fibers in the region of the occipital lobe to the opposite visual

cortex through the splenium; (2) dual blood supply to the macular cortical area from the middle and posterior cerebral arteries; (3) extensive macular representation throughout the entire striate area, and (4) tendency of a patient with loss of half the macular field to fix slightly to one side of the fovea, using a functioning paramacular area.

Book Reviews

Neurology of the Ocular Muscles. By David G. Cogan, M.D. Price, $6. Pp. 229, with 121 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

In this admirable text the author has made an effort to set forth clearly the state of present knowledge of the clinical physiology of the ocular motor system and the conclusions that can be safely drawn from the facts available.

Confronted with a neuro-ophthalmologic problem, one must note all obvious objective signs, elicit less apparent signs and correlate these findings with the known anatomy and physiology of the nervous system to evolve a clinical concept. The author has accomplished this goal after the manner of a lecturer and true research worker. He has analyzed problems personally encountered in one of the largest and most active neurologic services in the country, in the light of the physiology and anatomy recorded in the literature. Every conclusion is documented either by personal experience or by experiments and thorough review of the literature.

This analysis was originally formulated into a manual of instruction for graduate students. It has no doubt been revised many times before being organized into the present text, published for the benefit of ophthalmologists, neurologists, students and lecturers.

The author has condensed the information from many articles, each one of which would make long and tedious reading, into a few direct statements that are clear and easily understood.

The illustrations are excellent. They present their point in as clear and obvious a manner as does the accompanying text.

The whole book, text and illustrations, is an excellent job of clarifying and simplifying in an interesting manner a wealth of material. It is so clearly and simply written that it could be read by students and be valuable to them before, as well as after, they had had preliminary training in the specialty of ophthalmology.

The information is extremely well indexed according to objective signs and is organized into nine chapters as follows: Chapter I considers the extraocular muscles relative to their special physiologic, pharmacologic and histologic characteristics. Chapter II considers the gross anatomy and action of the extraocular muscles in a manner far more concise and easily understood than do other, easily available texts. Chapter III discusses the tone of the extraocular muscles as it is affected by the labyrinth, proprioception, retina and higher centers. This chapter affords the basis for the author's discussion of nystagmus in chapter IX, which is, in the opinion of the reviewer, the outstanding chapter of the book. Chapter IV discusses the nerves supplying the extraocular muscles, their arrangement, physiology and clinical disturbances. Chapters V, VI and VII treat the supranuclear connections of the ocular motor system, discussing lateral, vertical, torsional and conjugate movements, and disjunctive movements of convergence, divergence and fusion. In this discussion the author's own experiences and

his correlation of the literature in relation to these experiences afford a practical scheme, which facilitates understanding of this complicated subject. The scheme is stimulating in that it challenges one to make additional observations that may prove or disprove the author's ideas. Chapter VIII discusses the pupil. Knowing the author's work on this subject, the reviewer was disappointed that this chapter was relatively incomplete. Chapter IX discusses nystagmus. This presentation is an outstanding feature of the book.

After careful study of the text, the reviewer has difficulty in finding anything to criticize. Failure to refer to Chavasse is probably explained by the fact that nonparalytic strabismus is purposely omitted. Nevertheless, the references to tone and ocular motor proprioception could include Chavasse's ideas on the subject, since these represent a point of view not accepted by the author, but not yet disproved, and held to be true by many physiologists.

We have here a practical and though-provoking book, which will be consulted whenever a problem of neurology of the ocular muscles arises. It will be especially valuable for lecturers on this subject and as a ready reference.

S. RODMAN IRVINE.

More Than Armies: The Story of Edward H. Cary, M.D. By Booth Mooney. Price, $5. Pp. 270. Dallas, Texas: Mathis, Van Nort & Company, 1948.

The subject of this biography was bred and born in Alabama. Soon after his graduation from the Medical Department of New York University, in 1898, he selected ophthalmology and otolaryngology as his fields of practice. In the course of fifty years he has risen, among other positions of importance, to the presidency of the Southern Medical Association, of the American Medical Association and of the American Academy of Ophthalmology and Oto-Laryngology.

No man in this country has fought harder to see that the ethics of the profession are maintained and to prevent the socialization of medicine. For years Dr. Cary was dean of the Baylor University College of Medicine, Dallas. This year he was voted one of the first citizens of Texas. The story of the life and times of a great leader will be found interesting and informative.

BERNARD SAMUELS.

Bulletins et mémoires de la Société française d'ophtalmologie: Sixty Years, 1947. Pp. 434. Paris: Masson & Cie, 1947.

These transactions of the French Society of Ophthalmology bring a report of the sixtieth meeting, which was held in Paris on May 20 to 22, 1947. The main theme, "Retinal Changes in Relation to General Diseases," by Prof. P. Bonnet, of Lyons, was issued separately, as is customary, and was reviewed in the ARCHIVES (**39:** 115 [Jan.] 1948). The opening session of the meeting was taken up with the discussion of this main topic, in which eleven members took part. The remainder of the program consisted in the presentation of fifty-nine papers, which covered a wide variety of ophthalmologic subjects, as shown in the following titles: "An Epidemic of Acute Dacryoadenitis" (Toulant, Benhamou and Foissin); "Contact Glasses" (Fritz and Bonhomme); "Relative Hemianopsia" (Thiébaut, Guillaumat and Brégeat); "Lym-

phatic Vessels of the Bulbar Conjunctiva Studied with Injections of Trypan Blue" (Busacca); "Primary Edema of the Cornea" (Paufique, Chavanne and Prost); "Nonperforating Corneal Grafting" (Paufique and Guy Offret); "Chorioretinitis in Cases of Retinal Detachment" (Busacca); "Importance of Ocular Changes in the Diagnosis of Toxoplasmosis" (Franceschetti and Bamatter); "Infusions of Blood in Recurring Retinal Hemorrhage in the Young" (Calmettes, Deodati and Tabarly); "Importance of the Study of the Retinal Vein in Certain Ocular or General Diseases" (Fritz); "Retinographic Observations" (Amsler and Neuenschwander); "Results of Nonperforating Cyclodiathermy in Hypertensive Uveitis" (Weekers); "Retinal Edema and Intravenous Use of Procaine" (Rouher); "Clinical Observations on Pernicious Anemia" (Schupfer); "Onchocerosis" (Appelmans); "Late Ocular Changes in Polymorphous Erythema" (Babel and Martin); "Orthoptic Clinic at the Lariboisière Hospital" (Hartmann and Braun-Vallon); "Action of Calcium on the Permeability of the Blood-Ocular Barrier" (Amsler and Huber), and "Intraocular Injections of Penicillin" (Dubois-Poulsen and Miller).

The return of French ophthalmology to active participation in the progress of ophthalmology is a cause for general congratulation.

ARNOLD KNAPP.

Clinical Ophthalmology. By H. M. Traquair, M.D., F.R.C.S., Edinburgh. Price, $9. Pp. 264, with 72 illustrations, including 8 colored plates. St. Louis: C. V. Mosby Company, 1948.

In this short manual, the author brings as much ophthalmology as the undergraduate and the general practitioner require to advise ophthalmic patients and to decide when the expert is to be called in. Consequently, the common conditions have been described, and those aspects of ophthalmology which require specialistic training, such as refraction, examination of the eyeground and operations, are omitted. An interesting and unusual feature is the emphasis placed on the complaint and symptoms of the patient. The importance of a careful history is frequently overlooked in the completeness of the objective examination of ophthalmic patients and the mechanical perfection of the various instruments which are now in general use. Dr. Traquair's readable book is a wholesome reminder of the value of these features and the necessity of a broad medical outlook in the examination of an ophthalmic patient. The exposition of ocular pain and of headache, asthenopia and giddiness, and the chapters on impairment of sight without obvious external signs, on functional ocular manifestations and on misconceptions and prejudices will be found interesting and instructive. These sections can be read with profit by the practicing ophthalmologist. The book, in fact, is a most useful supplement to the usual ophthalmologic text.

ARNOLD KNAPP.

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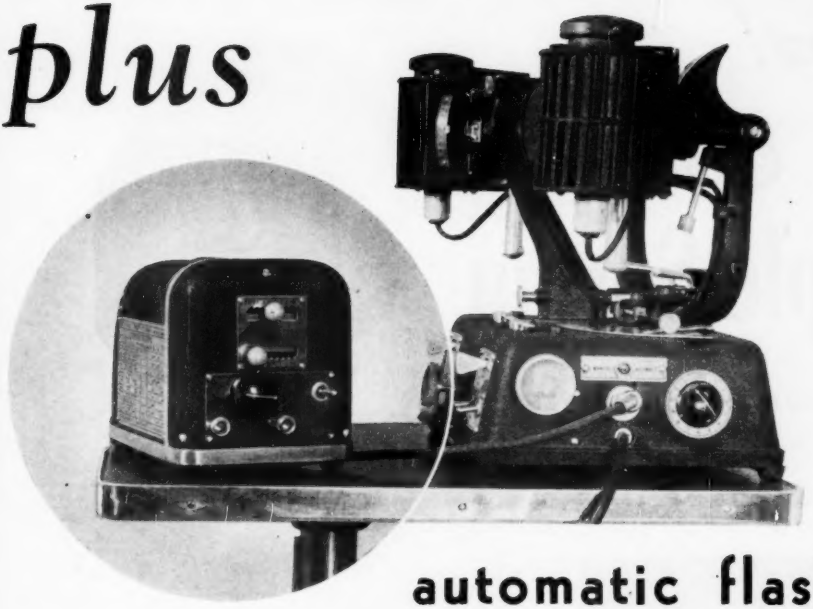

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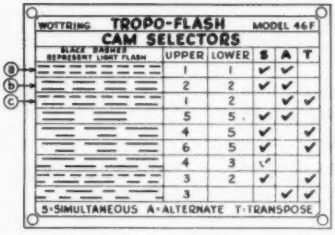

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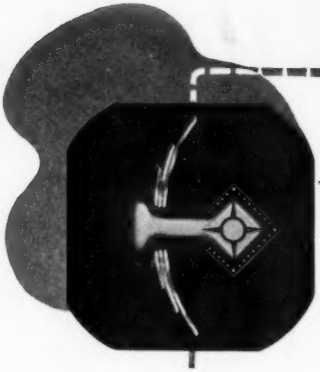

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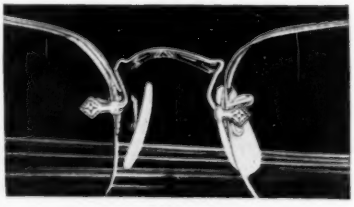

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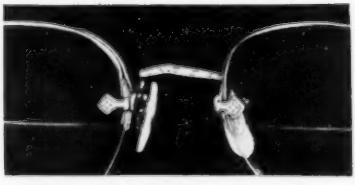

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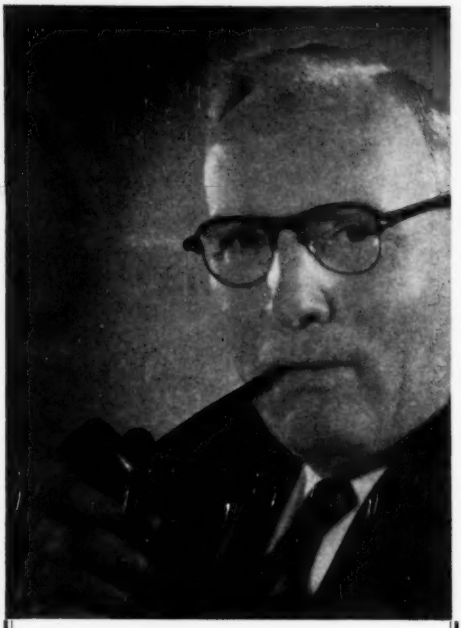

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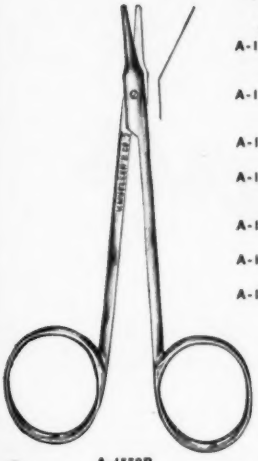

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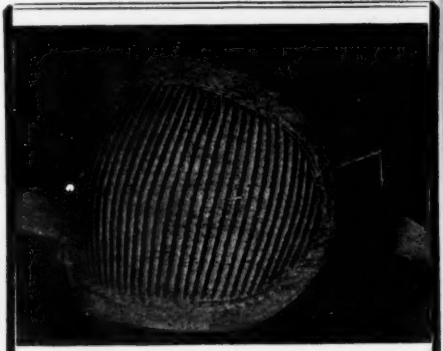

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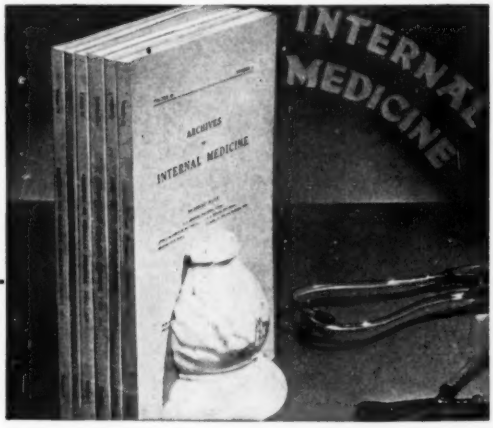

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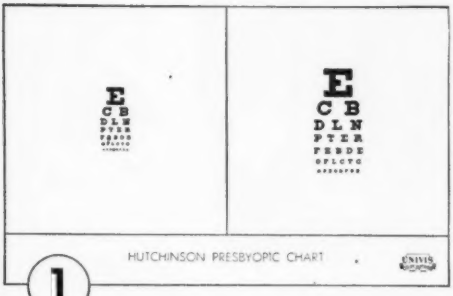

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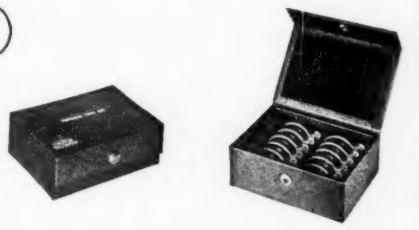

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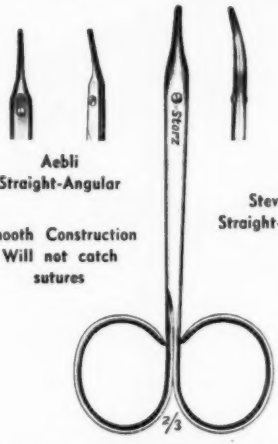

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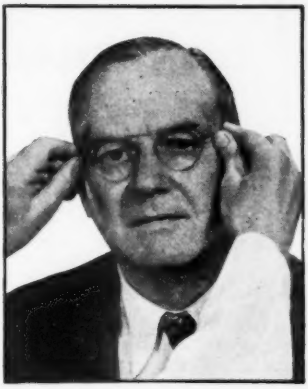

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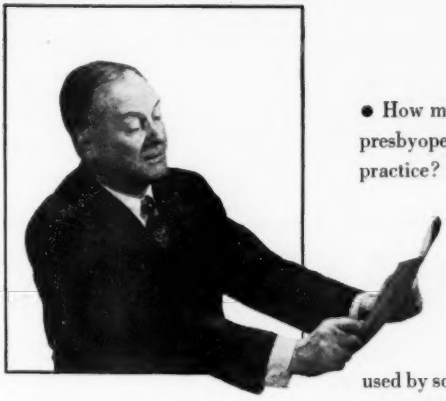

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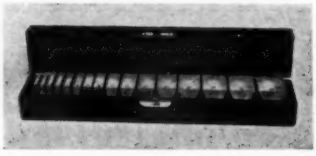

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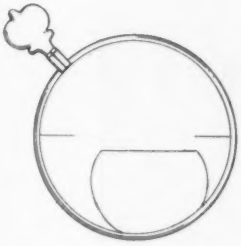

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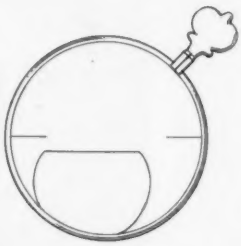

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